American Heart Journal

An international publication for the study of the circulation

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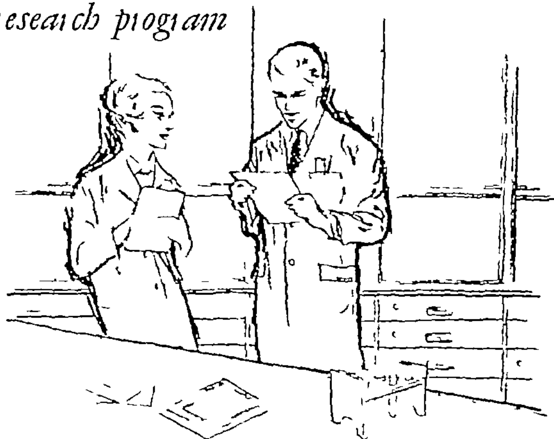
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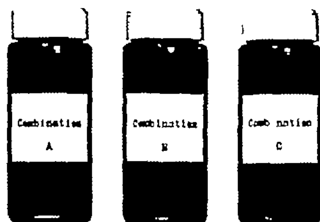


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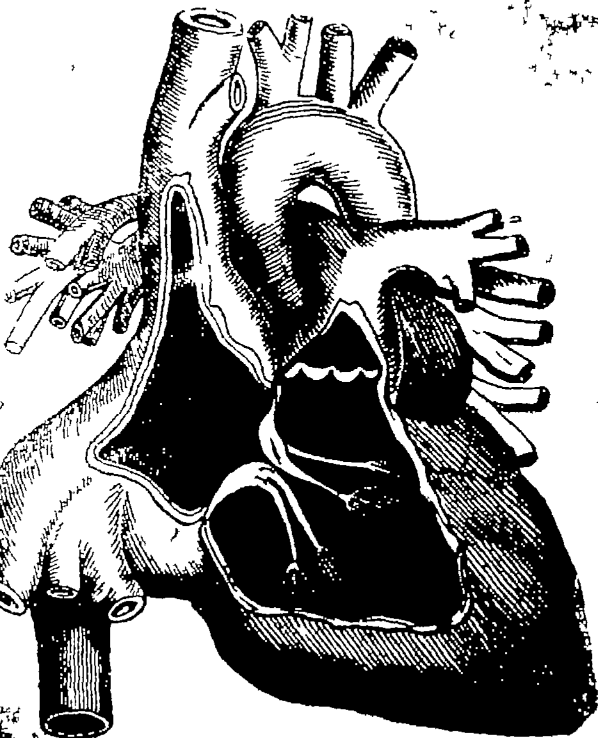
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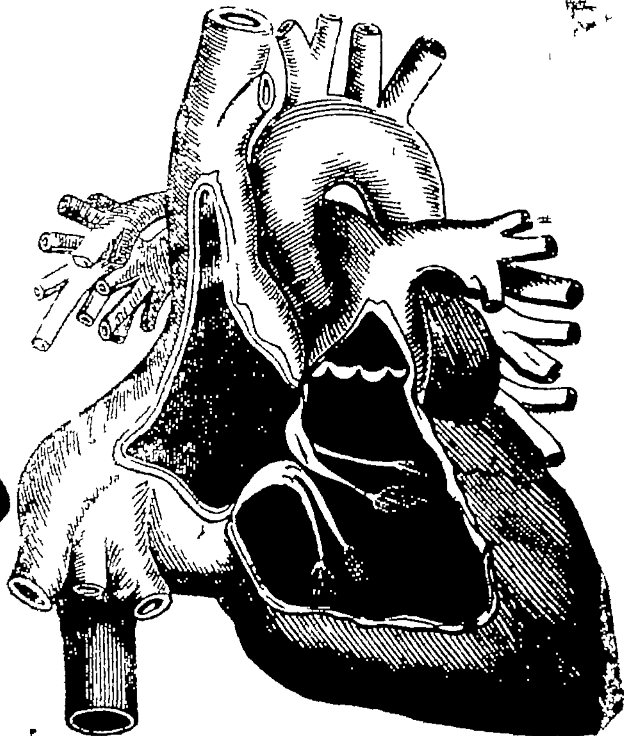
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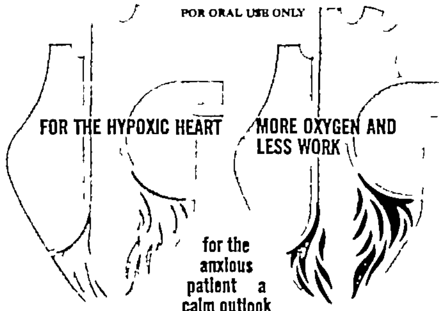
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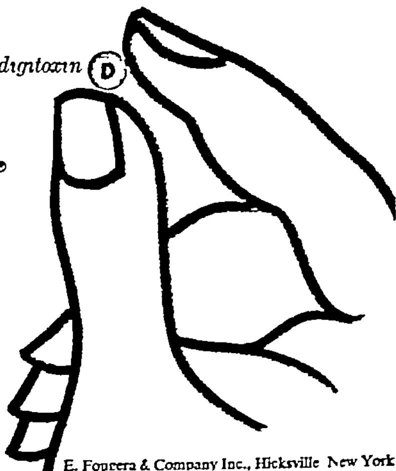
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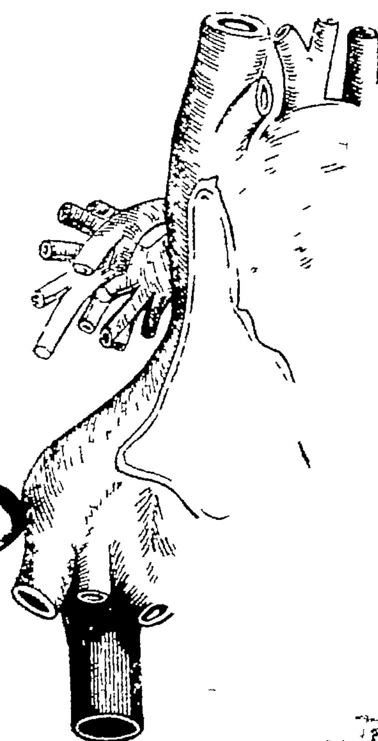
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When the rhythm

[illegible] has been available for [illegible] quinidine. Its particular [illegible] with quinidine. This [illegible] It is also effective [illegible] or for the control [illegible]

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When the rhythm is wrong...?

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q 12 h dosage anti arrhythmic

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American Heart Journal

January 1963 Volume 63 Number 1

Editorials

Special note

It is with great pleasure that the Board of Editors of the AMERICAN HEART JOURNAL introduce a new section with this issue of the Journal. This section entitled "Appraisal and Reappraisal of Cardiac Therapy," is directed by Dr. Arthur C. DeGraff who has been concerned with the therapeutic aspects of cardiology through all of his medical and cardiological career. In this section Dr. DeGraff plans to consider aspects of the current status of cardiac therapy for the readers of the Journal. Each monthly presentation will be a brief, succinct, and critical evaluation of the therapeutic agents and procedures which are currently employed in the field of cardiology. The presentations are intended to indicate clearly the opinions of Dr. DeGraff and his associates. Because of the rapid and constant changes in cardiology which make it difficult to keep abreast of all aspects of therapy, it is hoped that this section will be of value to our readers.

George F. Burch, Editor

What size mesh?

George G. Rowe, M.D.
Madison, Wis.

It is customary for a fisherman to select the mesh which he uses for his nets by the size fish he desires to take. Thus, if a large mesh is used, many smaller specimens will escape, whereas only the larger prey will be retained. Similarly, it is customary in a practice of medicine to eliminate from important consideration a host of minor complaints and physical findings as normal or borderline normal but to retain from them and the manner in which they are detailed an over-all impression which is helpful in the evaluation of an individual. The position of the cardiovascular consultant, however, becomes somewhat anomalous in that physical findings which he himself would ignore or defer judgment on, awaiting the clarification of time, are referred for definitive evaluation. Under these circumstances the consultant frequently finds himself in a position in which temporizing is inappropriate and with the alternatives of giving a categorical and relatively undocumented opinion that a physical finding is insignificant, or of proceeding through an extensive investigation

Associate Professor of Medicine, Cardiovascular Research Laboratory, The Department of Medicine, University of Wisconsin Medical School, Madison, Wis.
Received for publication April 13, 1962.

which may or may not be justified. It is realized that there are not answers to all questions, but some consideration of this problem as it faces the cardiovascular consultant may be helpful to the profession as a whole.

Let us consider an asymptomatic youth referred because of a heart murmur. The subject has already been evaluated by his own physician but the evaluation was obviously not completely satisfactory to all concerned and hence the referral for further study. Depending on how and by whom this patient has been evaluated, a considerable number of studies may already have been done. Surely basic re-examinations cannot be seriously questioned, and few would find fault under these circumstances with completion of a detailed history and physical examination which included an electrocardiogram and chest x-ray film. But already in these preliminary studies, decisions are involved as to the extent of the procedures. With many such subjects at the end of the routine history and physical examination the cardiologist will have made up his mind whether the murmur is or is not significant and the acquisition of x-ray films and an electrocardiogram are largely a form of insurance taken not for the benefit of the patient but in order to avoid any possible error or subsequent embarrassment to the cardiologist and to reassure the referring physician that an adequate study has been made. How complete should these studies be? Is a standard 12 lead electrocardiogram enough, or should vectorcardiograms also be made? Is a plain posteroanterior chest x-ray film adequate, or should films be made in the posteroanterior, lateral, and oblique projections during opacification of the esophagus? Should cardiac fluoroscopy be done, and is an ordinary fluoroscope satisfactory or is a fluoroscopic intensifier required? Shall the subject's heart sounds and murmur be graphically recorded? And if so, by a trained technician or by a seasoned physician who will take the time and effort to position the patient optimally, select the proper frequency response in the recorder, adjust the sensitivity of the recording device until the acoustic qualities which characterize the murmur are accurately recorded and extraneous sounds eliminated, insure use of the proper phase of respiration, relation to exertion, and cardiac rate, and do the host of things which separate an examination from a recording? Will the patient be specifically benefited by all these procedures? Or will the cardiologist? Surely some justification lies in the fact that as the experience and the acoustical acumen of the cardiologist are improved his opinion becomes more valuable and the benefit which accrues to all his patients becomes greater. In general, the indications that separate these procedures are quite well established, and since the only real risk involved is financial to the subject's family, the cardiologist will make these decisions as quickly as his training, experience, time and opportunity dictate.

The real questions concerning this subject involve more specialized procedures and frequently the decision is made more difficult because such techniques are available to the consultant but not to the referring physician. Indeed, it is not at all uncommon for such a subject to arrive with a note indicating that he is referred for a specific procedure, such as cardiac catheterization, and with the patient and his family already prepared for the study without any appreciation of either the procedure or the risks involved. Should the decision be made not to embark on such investigations, several possible consequences may ensue, many of which involve frustration to all concerned. Indeed, the decision not to study such a patient may only lead to his referral to another center at a greater distance and at greater expense, and with the perennial possibility that even though it is done farther away from home the procedure will not be carried out more expertly. Frequently, then, after considerable soul-searching, definitive evaluation is embarked upon in which the consultant finds himself with mixed feelings as to whether he is justified in his action. Nor have all the decisions been made when the definitive investigation is begun, for as instrumentation has advanced, the results are no longer delayed but become available as the diagnostic procedure unfolds, and a series of new decisions must be made as the study progresses.

It is inherent in the principles of the

indicator-dilution curve that the smaller the diluting volume, the more rigidly set is the morphology of the curve and hence in general the closer to the site of the lesion an indicator is injected and the closer to the point of recirculation regurgitation or venoarterial shunting the sampling is done the more exact will be the method Thus, injection of indicator into a peripheral vein followed by recording of its dilution curve from the lobe of the ear will be adequate to reveal shunts of considerable size Sharper definition of abnormalities will be obtained by direct recording of the curve obtained during aspiration of arterial blood through a suitable cuvette Progressively more central injections passing successively through the right side of the heart to the pulmonary wedge position and on into the chambers of the left side give clearly improving definition of left to-right shunts. Similarly an increase in definition should be produced by sampling from the artery at sites progressively closer to the heart and at progressively more rapid rates of withdrawal of blood Thus, the sharpest possible indicator-dilution curves, with the smallest central volume and hence the most clear-cut differentiation of the initial curve will accentuate whatever abnormalities are engrafted upon this curve.

But let us return to our patient who presents the imminent possibility that routine right heart catheterization will not reveal any defect and the diagnosis still remain in doubt How much doubt must remain in the mind of the investigator before he embarks upon further study? It is clear that insertion of a second cardiac catheter followed by injection of indicator into the distal portion of the pulmonary artery with inscription of indicator dilution curves simultaneously from blood withdrawn from a peripheral artery and that aspirated from a catheter in the right side of the heart, will detect left to-right shunts which cannot be found by the more simplified procedures described previously It is also reasonable to expect that if a catheter is introduced into the left side of the heart for injection of indicator or if such an indicator is inhaled (hence effectively injected into the capillaries of the lung) still further sharpening of the diagnostic measures will be attained and that this can also be combined with simultaneous arterial and right heart dilution curves. In general each additional procedure adds further instrumentation lengthens the study adds to the dose of radiation received by the subject and the investigator and increases the risk of arrhythmia tangled or knotted catheters febrile reactions, and infection And each increases the sensitivity of the diagnostic procedure

The problems concerning radiographic visualization of the defect with contrast substances are amenable to a similar type of analysis. In general the systemic cardiovascular reaction to intravenous injection of 1 ml of physiologic saline solution per kilogram of body weight is undetectable Similarly barring specific sensitivity the slow injection of a dilute solution of a contrast substance produces relatively little response and the more peripherally in the venous system such an injection is given the less will be the over all reaction On the other hand the more concentrated the contrast material the more rapidly it is given and the greater the proximity of its injection to the site of the abnormality the clearer will be the definition of the lesion In order to secure such definition the investigator uses progressively larger hence more rigid catheters higher injecting pressures and more radiographic exposures per second hoping for maximum clarity Furthermore, whereas observation in one plane will supply considerable information about a specific lesion the more projections in which such a lesion is viewed the clearer will become the over-all picture and the greater is the assurance that not only is the primary lesion revealed but also associated or unrelated abnormalities Again the investigator must balance the need for facts against the risks involved and here the risks become even greater than in standard diagnostic catheterization with sensitivity reactions, acute prolonged arrhythmias, and penetration of the cardiac chambers and injection of contrast material into the cardiac muscle and/or pericardial sac assuming ever-increasing significance

Eventually in such an asymptomatic subject catheterization of the right side of the heart may prove inadequate and

catheterization of the left side may also be embarked upon But again a new series of decisions is faced Will simple left heart puncture supply adequate information or must a catheter be passed through the puncturing needle Will injection of contrast substance be required Should the left heart be entered through transseptal puncture or will the catheter as it frequently does during injection into the left ventricle regurgitate into the atrium and make evaluation of mitral valve competence difficult or impossible Should the left ventricle be catheterized retrograde through the aortic valve And if so will it be adequate to do this procedure utilizing the Seldinger technique which therefore demands that it be done with an open-end catheter Such catheters are prone during high-pressure injections to regurgitate from the chamber in which they are placed because of the jet through their open end Furthermore they would seem to increase the risk of direct injection of the contrast substance into the myocardium or penetration of their relatively sharp end through the endocardium Should an arteriotomy be done so that a closed-end catheter can be inserted in order to minimize the possibilities of regurgitation of the catheter and penetration of the muscle wall by the contrast substance Another factor to be considered is that it is more difficult to pass retrograde through the aortic valve a closed-end catheter of sufficient size to ensure adequate radiographic opacification of the left ventricle than it is to manipulate a Seldinger wire through the valve and thread a suitable catheter over it If an artery is entered surgically for insertion of a closed-end catheter even though it is resutured its loss is a calculated risk and since the right brachial artery approaches the ascending aorta more favorably than the left under many circumstances such a decision potentially involves ischemic damage to the right hand and arm. Furthermore the younger the subject especially in the pediatric age group the smaller the artery hence the greater is the risk of its loss and the more are the "man years" of disability potentially at stake

To each individual caught in the web of this editorial the decisions rest in a different frame of reference. In the mind of the youth is the all important decision concerning high school athletics. The parents are concerned with the economic and social considerations involving their child and his future career The referring physician embraces most of these considerations along with those of the immediate and future medical care of his patient as well as the problem of how the frequently apparently arbitrary opinion of the consultant will affect him in relation to his evaluation of the patient. The consultant according to his bent, may concern himself with few or many of these considerations but surely he must weigh the significance of the lesion against the risk required to define it and whether therapy will be directed differently not only by himself but by others when the diagnosis is established Furthermore he must consider how carefully the pathologic anatomy must be elucidated not only for today but for what his surgical colleagues will be able to do on some indefinite tomorrow

The commercial fisherman has long lived with the problem that he can obtain a mesh so fine that he is unable to market the product which he catches. It is a simple matter for him to enlarge the meshes, selecting material that he can sell Until recently the diagnostic mesh available to the cardiologist has been a coarse sieve indeed but as the flood of technical and scientific information bears down upon him he finds at his disposal a wealth of power which is indeed difficult to restrain direct or use in a reasonable fashion Age old impregnable barriers are penetrated Familiar limits are obscured One finds himself able to define with precision lesions which by present standards are too insignificant to require therapy or impossible to treat effectively It is not possible to be caught up in such a revolution without a vibrant thrill of excitement And not too well hidden in this excitement is a haunting fear and insecurity born of the inevitable series of accidents and misfortunes dependent upon such floods.

The treatment of refractory retention of fluid with oral L-arginine monohydrochloride and meralluride

Henry F. Migala, M.D.
Richard P. Lasser, M.D.
Charles K. Friedberg, M.D.
New York, N. Y.

Refractory retention of fluid presents a problem in the management of several clinical states and is most commonly encountered in patients with congestive heart failure and those with hepatic cirrhosis. The administration of acidifying chloride salts in such patients has been effective in restoring responsiveness to mercurial diuretics. Ammonium chloride,[1-4] calcium chloride, L-lysine monohydrochloride, and recently intravenous and oral L-arginine monohydrochloride have been used for this purpose.

The gastrointestinal irritation induced in a large proportion of patients given calcium chloride or ammonium chloride and the unpredictable absorption of enteric coated ammonium chloride has limited the usefulness of these two agents. Furthermore, the well-known hazards of ammonia intoxication preclude the use of ammonium chloride in patients with liver disease.[15-17] L-lysine monohydrochloride was recently introduced in the treatment of edema. Although it contributes to the ammonia pool and its use is associated with some gastrointestinal irritation, it has been found to be safer and more reliable for the production of hyperchloremic acidosis.[8-10]

L-arginine monohydrochloride is an amino acid with a molecular weight of 174 which, when combined with a single chloride ion, forms the L-arginine monohydrochloride used in this study. The compound is soluble in water and has a somewhat salty taste. It is readily ionized in the gastrointestinal tract, yielding the chloride, while the arginine enters the Krebs-Henseleit urea cycle as a precursor of ornithine,[13] and may therefore not contribute to the ammonia pool. In vitro studies related to the use of this drug in hepatic encephalopathy suggest that arginine stimulates the conversion of ammonia to urea.[14] It was thought, therefore, that L-arginine monohydrochloride would be a safer chloruretic acidifying agent to use in patients with hepatic dysfunction secondary to portal cirrhosis or severe congestive heart failure. The search for an acidifying chloruretic salt free from gastrointestinal side effects was another reason for this study.

The purpose of this paper is to report our experience with a therapeutic regimen consisting of oral L-arginine monohydrochloride and meralluride sodium (Mercuhydrin) in 15 patients with refractory retention of fluid.

From the Division of Cardiology, Department of Medicine, The Mount Sinai Hospital, New York, N. Y.
Aided in part by Grant No. H-153 from the National Institutes of Health, United States Public Health Service.
Received for publication April 13, 1962.
*This investigation was carried out during the tenure of a Postdoctoral Fellowship from the National Heart Institute, United States Public Health Service.

Table I

Patient and diagnosis	Weight (Kg)	A. Before L-arginine monohydrochloride: Urine Na (mEq/L)	Urine Cl (mEq/L)	Plasma Na (mEq/L)	Plasma Cl (mEq/L)	Venous blood pH	B. After L-arginine monohydrochloride: Urine Na (mEq/L)	Urine Cl (mEq/L)	Plasma Na (mEq/L)	Plasma Cl (mEq/L)	Venous blood pH	C. Postdiuresis: Plasma Na (mEq/L)	Plasma Cl (mEq/L)	Venous blood pH	Weight loss (Kg)
1. ASHD	56.8	43	41	137	101	7.39	31	63	143	125	7.29	147	114	7.36	5.0
2. ASHD	65.2	10	11	142	101	7.38	15	38	140	102	7.34	144	104	7.38	2.1
	63.6	19	20	144	104	7.38	29	75	144	106	7.31	146	98	7.42	3.2
3. ASHD	72.7	26	38	116	102	7.38	36	82	147	112	7.22	144	109	7.43	5.0
	68.2	19	31	147	103	7.40	28	68	152	116	7.28				7.2
	48.2	12	35	141	100	7.36	50	48	138	105	7.32				
4. ASHD	61.5	9	13	140	97	7.45									
5. RHD	55.6	5	10	134	87	7.38	34	86	128	90	7.28	135	92	7.40	5.7
6. RHD	43.6	10	13	144	92	7.41	12	58	144	101	7.30	146	95	7.42	5.0
7. RHD	63.2	5	8	140	100	7.46	29	116	144	102	7.40	145	103	7.42	0.9
	62.6	45	46	138	85	7.40	64	140	139	97					0.9
8. RHD	52.2	4	5	126	90	7.41	8	48	124	107	7.21	136	99	7.39	7.2
9. Congenital HD	22.7	30	50	133	88	7.48	46	72	144	101	7.40	144	90	7.42	2.6
	22.1	5	11	136	96	7.44	36	90	136	106	7.31	133	89	7.45	2.6
10. Idiopathic hypertrophy	64.1	26	25	140	94		46	115	141	101		139	97		4.1
11. Idiopathic hypertrophy	82.3	9	23	144	94	7.37			142	104	7.19				
12. Portal cirrhosis	51.5	6	23	134	99	7.38	68	125	139	104	7.26	141	102	7.39	4.1
13. Portal cirrhosis	68.5	31	48	131	83	7.46	15	173	139	112	7.18	146	96	7.35	8.2
14. Portal cirrhosis	66.8	10	12	132	99	7.45	14	154	140	109	7.38				7.2
15. Portal cirrhosis	64.1	38	46	143	100	7.40	48	134	146	108	7.34				2.7
Average values		18	25	139	96	7.40	31	93	140	106	7.28	142	99	7.40	4.3

ASHD: Arteriosclerotic heart disease. RHD: Rheumatic heart disease.

Material and methods

A total of 20 trials was carried out in 15 hospitalized patients. The patients were admitted to the study if they failed to respond with diuresis and loss of weight to a regimen of bed rest restriction of salt and water digitalis (when indicated) and injections of mercurial diuretics Four patients had portal cirrhosis with ascites. Eleven patients had congestive heart failure this was secondary to rheumatic heart disease in 4 to arteriosclerotic heart disease in 4 to idiopathic cardiac hypertrophy in 2 and to congenital heart disease in one a 7 year-old child

During the period of study the patients remained at bed rest and were weighed daily before breakfast Daily oral intake of fluid was restricted to 1,500 c c or less and sodium intake to 800 mg Twenty four hour outputs of urine were collected and measured For the first 3 to 5 days of observation no arginine was administered while the weight urinary output and urinary chlorides and other urinary and plasma electrolytes were studied During this control period mercurial diuretics were administered to confirm the lack of significant diuretic response Then 20 to 40 Gm. of the arginine compound was administered daily in two to four divided doses yielding a total of 95 to 190 mEq of chloride. This corresponds in potential yield of chloride to 5 to 10 Gm of ammonium chloride The dose of arginine was decreased to 10 Gm. daily i.e 47 mEq of chloride for administration to the one child in this study This daily dose was continued until the concentration of urinary chlorides exceeded 40 mEq per liter provided that excessive acidosis did not develop.

When the desired concentration of urinary chlorides was attained an organic mercurial diuretic was injected on 2 successive days in a dose of 2 ml In the 5 patients who were refractory to meralluride in spite of levels of urinary chlorides above 40 mEq per liter L-arginine monohydrochloride was administered in an attempt to further increase the chloruresis.

Palatability was enhanced when the arginine compound was administered in cold orange juice. It was in this form that it was used throughout this study

Precise studies of metabolic balance were not possible since all studies were performed on patients on the general wards. This however was not considered to be essential to the clinical assessment of this agent Concentrations of sodium potassium and chlorides were measured daily in urine and plasma throughout the period of study Determinations of venous blood pH were also made Blood urea nitrogen was measured once during the control period and again after the administration of arginine

Values of serum and urinary sodium and potassium were determined with an internal standard flame photometer Chlorides were determined using a chloridometer* Whole venous blood pH was measured with a Cambridge research pH meter

Results

Table I is a composite of the salient values of blood and urinary electrolytes during the control period (A) at the time of maximal chloruresis (B) and after diuresis (C) Of the 20 trials all but three were completed Arginine was discontinued after a single test dose of 20 Gm in Patient 4 because of severe diarrhea. Patients 3 and 11 died before meralluride was given (*vide infra*) The two trials in Patients 2 and 9 and the first two trials in Patient 3 were carried out 1 week apart The third trial in Patient 3 was made 5 weeks after the second trial.

Before L-arginine monohydrochloride The data recorded under Part A of Table I represent an average of three or more determinations obtained during the period prior to the administration of L arginine monohydrochloride

The average concentration of urinary sodium was 18 mEq L. ranging from 4 to 45 mEq L. The concentration of urinary chlorides averaged 25 mEq L. with a range of 5 to 50 mEq L. The concentration of urinary potassium averaged 88 mEq L. with a range of 37 to 138 mEq L.

Plasma sodium during the control period averaged 139 mEq L. One patient manifested moderate hyponatremia (Patient 8 126 mEq/L) and 5 had levels of plasma

*Cotlove chloridometer

sodium in the low normal range (Patient 5, 134 mEq./L.; Patient 9, 133 mEq./L.; Patient 12, 134 mEq./L.; Patient 13, 131 mEq./L.; Patient 14, 132 mEq./L.).

Plasma potassium averaged 4.9 mEq./L. (normal for our laboratory) and there were no patients in the study with either hypokalemia or hyperkalemia.

Plasma chlorides averaged 96 mEq./L. Hypochloremia (less than 90 mEq./L.) was present in 5 patients (Patients 5, 7, trial 2, 8, 9 and 13). The venous blood pH averaged 7.40, ranging from 7.36 to 7.48. The average of the blood urea nitrogen values determined prior to the administration of arginine was 19 mg. per cent with a range of 10 to 26 mg. per cent.

After L-arginine monohydrochloride. The values of plasma and urinary sodium and chlorides and whole venous blood pH after the administration of L-arginine monohydrochloride and prior to injection of meralluride are recorded in Part B of Table I. The concentration of sodium in the urine rose to 31 mEq./L.—almost double that of the control period. The concentration of chlorides in the urine rose to 73 mEq./L., which represents an increase of 3 times the control level. The lowest value of urinary chloride concentration achieved was 38 mEq./L., whereas the highest was 143 mEq./L. A significant rise in urinary chlorides was thus attained in all trials. Urinary excretions of potassium remained essentially unchanged from the control phase (average 86 mEq./L.).

Values of plasma chlorides rose to an average of 106 mEq./L., which was 10 mEq./L. higher than during the control period. The highest concentration observed was 125 mEq./L. All patients experienced a rise in plasma chlorides. Venous blood pH declined on the average to 7.28 from the control value of 7.40 and decreases were noted in every patient. The lowest pH value observed was 7.18. Values of plasma sodium and potassium remained essentially the same as during the control period.

There was no significant change in weight during the administration of L-arginine monohydrochloride and no change in blood urea nitrogen was observed.

SIDE EFFECTS. Abdominal cramping and mild to moderate diarrhea occurred in 6 patients but did not necessitate interruption of treatment. Severe diarrhea after only a single test dose of 20 Gm. occurred in one patient (Patient 4) and necessitated discontinuation of the regimen. Bleeding in the lower intestinal tract occurred in Patient 5. This was preceded by mild diarrhea on the second and last day of administration of L-arginine monohydrochloride. The patient was also receiving corticosteroids and anticoagulant drugs at this time and prothrombin values were elevated to the generally accepted therapeutic range (23 to 25 seconds with a control of 12 seconds).

Two patients died while receiving the drug. One (Patient 11) had idiopathic cardiac hypertrophy and developed irreversible ventricular tachycardia. This arrhythmia had occurred several times previously but had responded to procaine amide. He had received a total of 40 Gm. of L-arginine monohydrochloride over the preceding 48 hours. Death occurred suddenly and unexpectedly in Patient 3. This patient had long-standing diabetes mellitus and coronary artery disease with severe congestive heart failure. She had previously had two successful and uncomplicated courses of this drug and received 30 Gm. of L-arginine monohydrochloride over a period of 36 hours prior to death.

Autopsies were performed in both patients and revealed congestive heart failure. A nonocclusive recent thrombus was found in the anterior descending branch of the left coronary artery of the first patient. No direct precipitating cause of death was found in the other patient.

Postdiuretic phase. Part C of Table I shows the loss of weight which resulted from two injections of meralluride on successive days and the values of blood electrolytes on the morning of the third day.

Total loss of weight achieved by 2 successive days of administration of meralluride averaged 9.46 pounds (4.3 Kg.) with a maximum loss of 18.0 pounds (8.2 Kg.) and a minimum loss of 2.0 pounds (0.9 Kg.). All of these patients, who were previously refractory, experienced a significant diuresis. Loss of weight ceased after the second injection of meralluride despite the fact that visible edema was

still present in a few patients and further injections of meralluride did not provoke renewed diuresis until acidosis was restored by further administration of arginine. Whereas most patients were restored to dry weight by a single therapeutic regimen others required repetition of the complete cycle.

Studies of blood electrolytes were obtained in 13 of the preceding 20 courses of therapy 24 hours after the second injection of meralluride The concentration of potassium in the plasma was essentially unchanged from previous levels. The concentration of plasma sodium showed a slight rise above control levels whereas the concentration of plasma chlorides decreased by an average of 7 0 mEq /L. from levels extant at the peak of the administration of arginine hydrochloride and remained slightly higher than during the control period

After diuresis venous blood pH returned to the levels recorded prior to the administration of arginine indicating that discontinuation of L-arginine monohydrochloride and the diuretic response to the meralluride had resulted in complete correction of the acidosis in 2 days.

Discussion

The above-described findings have essentially confirmed those reported by Manning and Delp who found that L-arginine monohydrochloride orally administered is a satisfactory chloruretic and acidifying agent. Its administration before the use of mercurial diuretics in patients with refractory retention of fluid restores the effectiveness of response to mercurials and potentiates their action. The side effects encountered in our patients were perhaps more frequent and of greater severity than previously reported The diarrhea encountered was usually mild to moderate, but was severe in one patient and was associated with bleeding in the lower intestinal tract in another Thus, only half the daily dose was administered on the first day throughout this study

Death occurred in 2 patients while they were receiving L-arginine monohydrochloride The immediate cause of death did not appear to be directly related to the use of this drug

No essential difference in the degree of response was noted between patients with congestive heart failure and those with cirrhosis.

The daily dosage used in this study was arbitrary and was chosen because experience with other acidifying agents indicated that about 200 mEq of chlorides a day was usually necessary to produce adequate chloruresis in 2 to 5 days.[13] However some patients required more or less than the others and the best indication of adequate dosage was always the daily 24-hour concentration of chlorides in the urine The recommended levels of 40 mEq L. do not guarantee a good response to mercurials. Several patients in this study were refractory with higher initial levels and responsiveness was re-established only after greater chloruresis and acidosis had been induced Although metabolic acidosis was produced in all patients, it was never severe enough to be symptomatic. Of course L-arginine monohydrochloride like other acidifying agents, should be administered only with the greatest caution in patients with pre-existing acidosis.

The mechanism by which this agent potentiates the action of mercurials is not completely clear However acidosis and hyperchloruria are known to be important in this respect. [8] The failure of some patients to undergo adequate diuresis in spite of elevated urinary chlorides and metabolic acidosis is an indication that other important factors are also operative in refractory retention of fluid

The slight diuresis observed in some of the patients receiving arginine alone may indicate that this drug is itself a mild diuretic No studies were performed to establish this diuretic property and its possible mode of action Because L-arginine monohydrochloride is believed to stimulate the conversion of ammonia to urea the suggestion was made that the increased blood urea nitrogen so produced could act as an osmotic diuretic [7] No significant change in blood urea nitrogen after administration of this drug was observed in this study The slight diuresis seen in some of the patients prior to the administration of meralluride is more probably related to the mild diuretic action of similar acid producing salts.

Previous studies of a similar nature carried out using another acidifying agent, namely, L-lysine monohydrochloride, demonstrated essentially the same features of chloruresis and acidosis shown in the current study.[14] There appears to be no difference in the two drugs with regard to the rapidity of effect, the levels of concentration of chlorides in the blood and urine, and the diuretic response to subsequent injections of meralluride. L-arginine monohydrochloride may theoretically be safer than L-lysine monohydrochloride in patients with hepatic disease. It is our impression, however, that the former compound, when administered orally, is associated with a higher incidence of gastrointestinal side effects. Therefore, our data do not suggest that L-arginine monohydrochloride has any practical advantage over L-lysine monohydrochloride.

Summary and conclusions

L-arginine monohydrochloride was given orally as an acidifying chloruretic agent before the administration of mercurial diuretics in patients with refractory retention of fluid due to congestive heart failure or hepatic cirrhosis. A total of 20 trials was carried out in 15 patients.

A total daily dose of 20 to 40 Gm., given in divided doses for 2 to 4 days, was effective in all cases in producing metabolic acidosis and in raising 24-hour levels of urinary chlorides from a pretreatment average value of 25 mEq./L. to 93 mEq./L.

Of the 20 trials, 17 were completed. Injection of 2 c.c. of meralluride on 2 successive days after administration of L-arginine monohydrochloride resulted in an average loss of weight of 4.3 Kg. (range 0.9 to 8.2 Kg.) and a correction of the acidosis.

Mild to moderate diarrhea occurred in several patients after the administration of this agent. The death of 2 patients while they were receiving arginine and the bleeding in the lower gastrointestinal tract which occurred in another patient did not appear to be directly related to the use of this drug.

L-arginine monohydrochloride is a reliable acidifying chloruretic agent and effectively potentiates the action of mercurial agents in cases of refractory retention of fluid. The gastrointestinal side effects, however, were more frequent and of greater severity than in the only other reported study on the use of oral L-arginine monohydrochloride in refractory edema.

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Cor triatriatum

Correlation of clinical and autopsy findings in 3 cases

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Cor triatriatum is a rare congenital heart malformation amenable to simple corrective surgery A preoperative diagnosis is therefore of paramount im portance Very few cases so far have been diagnosed during life and to our knowl edge in no more than 9 cases has operation been successful

Because of the rarity of this anomaly and the diversity of the symptoms with which it may be manifested we wish to report 3 additional cases. In our discussion we have made an attempt to correlate the clinical and autopsy findings in these cases. It is noteworthy that in our third case the abnormal septum was found in the right atrium. Only 4 such cases have been reported previously

Case reports

Case 1 A.X., 19-month-old male infa t wa admitted to the Pediatric Clinic of the University of Athens, with a history of fever anorexia, nd f ilure t thrive. The infant weighed 3,800 grams t birth, and his development during the first year of lif was said t be normal. The patient thereafter developed ttacks" of dyspnea, which were aggravated in the last 2 months prior t his admission. Physical examination revealed slightly cyanotic hild with marked respiratory distress. The heart wa enlarged to percussion nd palpa tion. The pulmonic component of the second sound w s accentuated. A Grade 2 3 short y tolic mur mur was best heard over the left upper ternal border The lungs had moist râles bilaterally The liver was enlarged 3 fingerbreadth below the right costal margin. The peripheral pulses were well palpable. The rest of the examination was not contributory A chest roentgenogram showed a enlarged heart and a prominent pulmonary conus (Fig 1). The electrocardiogram indicated right trial enlargement and right ventricular hyper trophy of marked degree. The patient was digitalized nd oxygen, diuretics, nd ntibiotics were administered. However his condition deteriorated rapidly nd he died on the second hospital day

At autopsy the left trium was found t be divided by an anomalous diaphragm into two chambers. The mediosuperior chamber received all the pulmonary veins and had the shape of an i erted truncated cone. It superior surface measured 2.8 by 3 0 cm and its inferior surface 1 4 by 1.2 cm. I the diaphragm were two openings, bout 0 7 and 0.2 cm. i diameter which communicated with the inferior true left trium. Another small opening, about 0.3 cm. in diameter led the proto int the right trium (Fig 2), which w dilated. The left trium was of normal size. The right ventricle was dilated and hypertrophied the anterior wall wa bout 7 mm. in thickness. The w ll of the left entricle also measured 7 mm. The valves ere regular

Case 2 P.S., 8-month-old boy was first seen in Cook County Children Hospital, Chicago, at the ge of 2 months because of pneumonia. Since then the child wa said t ha e been slightly blue and to have had repeated respiratory infec tions. On examination, his kin had dusky color but no clubbi g or definit cyanosis were present The heart was enlarged to palpation. The pulmonary closure of the second sound w accentuated A Grade 2 3 hort systolic murmur wa best heard over the third t fourth left intercostal paces. A

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Fig. 1 Case 1 Chest roentgenogram, postero-anterior view

thrill was palpable and the femoral pulses were normal. Chest x-ray examination showed an increased cardiac shadow with a prominent pulmonary artery (Fig 3). The lung fields appeared to be somewhat congested. The electrocardiogram indicated marked right atrial enlargement and right ventricular hypertrophy. A venous angiocardiogram was made. The right atrium was dilated and remained opacified during levoangiocardiography. No other anomalies were detected. An atrial septal defect or anomalous venous drainage was suspected clinically. A surgical exploration was attempted; only a large septal defect was found and this was closed. Two days later the patient died.

At autopsy the left atrium was found to be separated into two chambers by an abnormal diaphragm. The upper accessory chamber communicated with the right atrium through a large septal defect, and with the left atrium through an opening in the diaphragm. As seen in retrospect, this opening was mistaken for the mitral valve by the exploring finger of the surgeon.

Case 3 J.F. A 7-month-old female infant was admitted to the Pediatric Cardiology Department of Cook County Hospital, Chicago, because she had had dyspnea and cyanosis since the age of 6 weeks. On physical examination the infant appeared to be dyspneic and mild cyanosis was present in both the upper and the lower extremities. The cardiac apex was felt over the fifth left intercostal space and at the mid-clavicular line. There was a loud pulmonary closure sound over the second and third left intercostal spaces. A Grade 3 systolic murmur accompanied by a thrill was best heard in the same area. Chest x-ray films revealed an increased diameter of the heart and convexity of the heart shadow in the pulmonary area. The electrocardiogram was suggestive of right atrial enlargement and biventricular hypertrophy. The patient was catheterized, and the data are shown in Table I. The patient subsequently died of pulmonary infection.

At autopsy the heart was found to be enlarged, particularly the chambers on the right side. The right atrium was divided into two compartments by a partially fenestrated fibrous diaphragm, which was attached to the endocardial surface of the posterior lateral portion of the right atrium. The inferior compartment received both venae cavae in a normal manner and contained the auricular appendage, which was dilated. There were two defects, one above and the other below the diaphragm, in the septum primum, measuring 0.8 by 0.5 cm. and 1.0 by 0.8 cm., respectively. These communicated with the left atrium. The foramen ovale was closed. All the pulmonary veins entered a sac-like venous sinus which communicated with each atrium through a small ostium. The tricuspid orifice had a circumference of 5.7 cm. and the right ventricle was hypertrophied. The chambers of the left side of the heart were otherwise normally formed. The ductus was closed.

Discussion

Niwayama[8] in a critical review of the literature prior to 1960 found only 38 cases reported to which he added 5 of his own. Since then about 11 cases have been recorded[4, 9-12] which brings the total number to 54.

The majority of recent workers support the explanation suggested by Griffith[13] namely that early embryology is responsi-



Fig. 2 Case 1 Posterior view of the heart. The pulmonary veins (PV) enter the accessory atrium (CPV). The vertical probe ( ) is inserted through an opening from the accessory atrium into the left atrium. The probe (b) leads into the right atrium. The number 2 is at the orifice of the removed inferior vena cava.



Fig. 3. Case 3. Chest roentgenogram, posteroanterior view.

ble for this anomaly. According to this view the third atrial chamber which exists in this malformation represents, in fact, a dilated common pulmonary vein which failed to be incorporated into the left atrium. In cor triatriatum an abnormal septum (diaphragm) divides the left atrium (or rarely the right) into two separate chambers which usually communicate through a narrow opening. The upper (accessory) atrium receives all the pulmonary veins and the lower (true) atrium contains the atrial appendage and the mitral (or tricuspid) valve. In the most common cases the opening of the anomalous septum is small and produces considerable obstruction to the pulmonary venous return. The smaller the size of the communication, the earlier the symptoms will appear. In about two thirds of the reported cases death occurred during the first 2 years of life. However, if the fenestration is very large, no obstruction at all will occur and these patients live to adult life.[18] In some patients there were multiple fenestrations in the septum, and in 3 cases, none.[9] In such instances an anomalous venous drainage or defects above and below the septum are essential for survival. In 4 patients the abnormal diaphragm was found in the right atrium and here is supposed to represent a persistent right valve of the sinus venosus.[18]

There appears to be a goodly number of anatomic variants of this anomaly depending on the presence or absence of interatrial communications which may further complicate the clinical features. If, for instance, no interatrial communication exists and the exit from the accessory chamber to the left atrium is stenotic, the hemodynamic alterations and clinical manifestations may be similar to those of congenital mitral stenosis, stenosis or atresia of a common pulmonary vein, or endocardial fibroelastosis of the constrictive type [illegible].[4] If an interatrial communication exists (open foramen ovale or atrial defect) between the accessory chamber and the right atrium, only a left-to-right shunt will occur, imitating an atrial septal defect and, in more severe cases, a Lutembacher complex.[4] In case of a large communication between the lower (true) atrium and the right atrium, a right-to-left shunt may occur, and if both upper and lower chambers communicate with the right atrium, the flow may

Table I. Catheterization data from right side of heart in Case 3

	Location					
	SVC	*IVC*	*RA*	*RV*	*LA*	*FA*
Oxygen content (vol. %)	9.1	11.8	14.8	15.3	15.4	15.1
Pressure (mm. Hg)	—	—	(4)	66/1	(7)	105/60
Oxygen saturation (%)	—	—	—	—	88.6	86.5
Oxygen capacity (vol. %)	17.4					

SVC, Superior vena cava; IVC, Inferior vena cava; RA, Right atrium; RV, Right ventricle; LA, Left atrium; FA, Femoral artery.

be bidirectional. Then a clinical cyanosis may appear in proportion to the degree of unsaturated blood passing into the systemic circulation. Furthermore, if the abnormal septum is located in the right atrium, as in our third case, the condition may imitate an atrial septal defect with a right-to-left shunt or an anomalous venous drainage, depending on the interatrial communications. The clinical picture can be still more complicated if additional heart anomalies are associated.[4-]

The most commonly reported manifestations in cases of cor triatriatum were attacks of dyspnea and pulmonary edema, enlargement of the right side of the heart, and congestive heart failure. Analysis of the auscultatory findings in our 3 cases revealed a short systolic murmur over the upper left parasternal area and an accentuated pulmonary closure in all. Nonspecific murmurs and accentuation of the second sound have been noted in previous reports.[13] The roentgenographic and electrocardiographic findings in all our cases were suggestive of marked right ventricular (biventricular in the third patient) hypertrophy and right atrial dilatation. The pulmonary vascular markings and pulmonary conus were prominent; this is also commonly described in the literature.

Venous angiocardiography, which was performed in our second patient, was not of definite help. There are not many angiocardiographic reports, but we believe that the techniques of cineangiocardiography from the pulmonary artery can be of some value in the diagnosis of cor triatriatum if this condition is suspected. Catheterization of the right side of the heart of our third patient (Table I) showed an increased oxygen saturation in the chambers of the right side of the heart which was approximately the same as the oxygen saturation of the left atrium and the systemic circulation. These findings could be compatible with a total anomalous venous drainage. The pressures in the right and left atria were about normal. We were not able to measure the pulmonary wedge pressure at that time. It has been shown, however, in previously catheterized patients that the arterial pulmonary wedge pressure when measured was always found to be elevated.[2, 4-11] If we had been able to demonstrate a markedly increased wedge pressure in contrast to the presence of normal atrial pressures (Table I), it would have been almost diagnostic for the disease because it is obvious that only an obstruction between the pulmonary arterioles and the "true" atrium could explain the difference in these pressures.

In the supradiaphragmatic type of anomalous venous drainage the pulmonary wedge pressure is usually normal or slightly elevated. However, in the infradiaphragmatic type a high pulmonary wedge pressure is anticipated, but the prominent cyanosis, the more severe symptoms, and the conspicuously small size of the heart are points for differentiation of this lesion. In some rare complicated cases with stenosis of the pulmonary veins without an intracardiac anomalous septum, the final diagnosis can be made by catheterization. In such a case this diagnosis was made by passing the catheter into the left atrium, in which a normal pressure was found, and then into a pulmonary vein, in which a high pressure was recorded.

In conclusion, cor triatriatum can be greatly suspected during life if signs and symptoms of pulmonary venous and arterial hypertension exist and a high pulmonary wedge pressure is proved. Demonstration of a pressure difference between the left atrium and pulmonary arterioles (if these locations are accessible to the catheter) is the best evidence for this malformation.

The surgical treatment consists of enlarging the opening in the abnormal septum. This can be accomplished easily without much risk, and can be a lifesaving procedure.

Summary

We have reported the clinical and autopsy findings in 3 cases of cor triatriatum. We discussed the possible variants of this anomaly and their clinical features. The most common manifestations include a nonspecific systolic murmur, accentuation of the second sound, right ventricular hypertrophy or failure, pulmonary congestion, and the demonstration of an

elevated pulmonary wedge pressure by cardiac catheterization If at the same time a normal left atrial pressure can be obtained this is diagnostic for the disease. In any case in which cor triatriatum is suspected a cardiotomy should be at tempted with the purpose of correcting it surgically This may be a lifesaving procedure

The senior thor is indebted to Dr B M Gaml for his permission to in lude cases seen in his department

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Electrocardiogram in hypopituitarism
Reversibility of changes during treatment

Jerzy Kosowicz, M.D.
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Electrocardiographic changes associated with hypopituitarism have been given little attention in textbooks of endocrinology and electrocardiography, but the articles of some authors indicate that electrocardiographic abnormalities in cases of this disorder are of high incidence. Sheehan and Summers, having studied electrocardiograms in 20 cases of pituitary insufficiency, suggested that these changes were similar to those in myxedema. Whittaker[3] reviewed electrocardiograms in 9 cases of hypopituitarism and found flattening of T waves and low voltage of QRS complexes. Querido, in the electrocardiograms of 10 patients, also observed ST-T abnormalities in 9 cases and low voltage in 3 cases.

Electrocardiographic patterns in hypopituitarism were reported by some authors to be similar to those in hypothyroidism, whereas others found them similar to those of adrenal cortical hypofunction. The reversibility of electrocardiographic changes during treatment is not yet fully clarified. Bernart and Andino[4] did not find any alterations in electrocardiograms after oral administration of 0.5 to 1 gram of desiccated thyroid to patients with post-partum hypopituitarism. Opposite results were reported by Beck and Montgomery,[5] who noted distinct electrocardiographic improvement in 3 patients on combined treatment with cortisone and doses of 2 to 3 grams of thyroid daily.

Our studies were performed in order to clarify whether electrocardiographic changes depend upon thyroid or adrenal cortical hypofunction. Moreover, our studies were intended to indicate whether electrocardiographic abnormalities are reversible during an adequate hormonal treatment of patients.

Material and methods

Twenty patients with typical hypopituitarism have been examined during the last 10 years. Of these, 11 were women and 9 were men, whose ages ranged from 22 to 63 years. The cause of pituitary insufficiency varied, but the majority of our patients had tumors arising from or damaging the pituitary gland. Six patients had chromophobe adenomas (verified at operation in 5 cases), 2 others had eosinophilic adenomas with long-lasting manifestations of acromegaly. Hypopituitarism in 2 patients resulted from a craniopharyngioma—in one case from meningitis, in another from a malignant tumor of the optic tract, and in still another from a cerebral hemorrhage in the region of optic chiasma. Three women had typical post-partum pituitary insufficiency (Sheehan's syndrome). Finally, 4 patients had hypopituitarism of unknown etiology.

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elevated pulmonary wedge pressure by cardiac catheterization If at the same time a normal left atrial pressure can be obtained this is diagnostic for the disease In any case in which cor triatriatum is suspected a cardiotomy should be attempted with the purpose of correcting it surgically This may be a lifesaving procedure

The senior uthor is indebted to Dr B M Gamil for his permission to include cases seen in his department

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the tested frequency range of 50 to 1,000 c.p.s.) which depends on the location of the sound receptor and generator and on the frequency of the test vibration

3 Cardiac action modifies the conduction of sound through the walls of the different heart chambers in a characteristic manner A sound wave of constant amplitude applied to the thoracic surface will be modulated in amplitude by heart action when it passes the heart walls. The tracing of the test vibration modulated in amplitude is called the *diacardiac phonogram* The shape of the diacardiac phonogram depends mainly on the heart cavity from which it is picked up It is affected only to a lesser degree by the location of the extra cardiac sound generator the frequency of the test vibration and the respiration. An increase in the distance of the sound generator from the receptor does not alter the shape of the diacardiac phonogram significantly but diminishes its mean amplitude.

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Left atrial arrhythmias

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Localization of ectopic atrial foci has received limited attention in the past. Therefore little is known concerning the differentiation between right and left atrial ectopic rhythms from the surface electrocardiogram.[1]

Previous studies of the P wave morphology associated with different atrial foci appear to be contradictory. Stimulation of the canine right atrium gave rise to an upright P wave in Lead I, whereas foci in the left atrium generally produced a negative P wave in Lead I, or occasionally an isoelectric inscription.[2] A similar study in patients undergoing thoracotomy failed to demonstrate P wave inversion in Lead I with either right or left atrial ectopic foci of any location, but occasionally the P wave was isoelectric in Lead I after stimulation of the caudal region of the left atrium.[3]

Atrial activation from left to right in dextrocardia is characterized by inversion of the P wave in Lead I.[4] Atrial arrhythmias which displayed this morphology have also been reported in patients with anatomically normal cardiac position. Therefore it seemed pertinent to investigate left atrial rhythm in the intact human being. The cardiac catheter with an electrode at the tip to record the intracardiac electrocardiogram can produce ectopic beats in the intact human being and localize precisely the ectopic focus when it arises beneath the exploring electrode.[8-10] In the present study the features of such experimentally produced left atrial beats are described. Also clinical electrocardiograms with similar features occurring spontaneously are presented.

Materials and methods

The subjects studied were 6 patients undergoing catheterization of the right side of the heart, in whom the left atrium was entered via an interatrial septal defect. The cardiac catheter with an electrode at the tip was positioned with the tip making gentle contact with the lateral or posterior wall of the left atrium. Location of the tip of the catheter within the left atrium was ascertained by meeting all of the following criteria: (1) fluoroscopy showed the tip of the catheter to be clearly to the left of the left vertebral border, (2) an atrial pressure pulse was recorded

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(3) blood sampled possessed an arterial saturation (4) the intrinsic deflection of the sinus P wave in the cavitary electrogram occurred during the second half of the simultaneous P wave in Lead I

With the tip of the catheter in contact with the left atrial wall premature contractions were produced by small discrete to-and-fro movements of the catheter tip A premature atrial contraction was considered to arise at the catheter-electrode tip only if the cavitary electrogram was entirely negative and began with a rapid intrinsic deflection Seventy-three premature left atrial contractions (LAPCs) met this criterion and form the basis for the experimental results reported below Other morphologies of the cavitary P wave were recorded by the catheter electrode but were not included in this report since the ectopic focus may have been generated by segments of the catheter other than the tip, and their accurate localization was not possible. In some cases, the lateral right atrial wall was similarly stimulated to obtain right atrial premature contractions for comparison

The intracardiac electrogram Standard Lead I and the atrial pressure contour were recorded simultaneously in 4 patients. In 2 patients, Lead V_F was also recorded on the simultaneous tracing

The 3 clinical cases illustrated were encountered in routine electrocardiograms† at The Presbyterian Hospital.

Results

P wave in Lead I Four morphologic types of P wave were seen in Lead I occurring with the 73 LAPCs reported herein *Type A* consisted of an entirely negative deflection (QS pattern) and was the most common morphology in Lead I it occurred with 52 LAPCs (71 per cent) *Type B* consisted of an initial major negative deflection followed by positive deflection of extremely small amplitude and brief duration (Qr pattern) This morphology was uncommon it occurred in only 6 instances (8 per cent) *Type C* consisted of an initial positive deflection of small amplitude and brief duration followed by a much larger negative deflection (rS pattern) This was the second most common morphology it occurred with 11 LAPCs (15 per cent) *Type D* consisted of a P wave which was essentially isoelectric being represented by an absent deflection or a barely perceptible undulation This morphology was rare among our observations it occurred in only 4 instances (5 per cent)

type	morphology	No	%
A		52	71
B		6	8
C		11	15
D		4	5

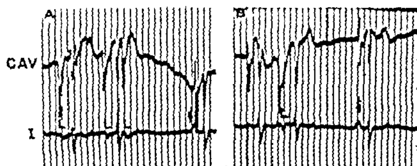
Fig 1 P-wave morphology in Lead I for 73 left atrial beats.

The four morphologic types of P wave in Lead I seen to occur with LAPCs are schematically drawn and the foregoing data summarized in Fig 1 These four morphologies are illustrated in Figs. 2 5 wherein their variations can also be seen.

P wave in Lead V_F Of the 73 LAPCs studied Lead V_F was recorded simultaneously with Lead I intracardiac lead and the pressure contour in 26 LAPCs. In these 26 beats, almost all combinations of *q r* and *s* deflections were seen in Lead V_F and no characteristic pattern emerged. However an extremely consistent feature of the P wave in Lead V_F was the low amplitude, which was generally less than 0 1 mv In these 26 instances the simultaneous recording of Leads I and V_F permitted calculation of the direction of the mean P vector in the Einthoven refer

*Electronics for Medicine recorder, †Sanborn Twin-Beam recorder.

$\frac{\Sigma P_{VF}}{\Sigma P_I}$ = arc tan (a) where ΣP_I and ΣP_{VF} are the net algebraic areas of the P wave in Leads I and V_F respectively and a is the clockwise angle subtended by the mean P vector and the positive limb of the Lead I axis.



F g 2 T sections of record during left timulation in Subject 1 S indic tes nsatrial beat nd L ndicates left trial beat Time lines 0 1 second In A the f st three trial beat originate in the left trium at the catheter tip electrode. The third is not conducted to the entricles In B three left atrial beat the itary I is entir ly negative nd begins with a pid intrinsic deflection *base equally rapid return tow rd the base line suddenly gives w y to a more* gradual slope t wh h poi t the P wa n Lead I commences. These three beat show mpletel negati I wa es in Lead I The last beat in A is of sino-trial orig The surfac I begi prior to the I wa from the left trial ty nd the trinsic deflection of the ca itar P wa e falls on the descending limb of the P w n Lead I I B the second beat is LAPC w th the P wa oc rri g near the end of the preceding T w v The relationship between tary I surfac I es for the LAPC nd the sinus beat are as described low

ence fr me The listribution of these directi ns i the frontal pla ie is shown in Fig 6 The great majority of mean I vect rs fell w thin a 90-degree sector lying between a ngle f 120 and 210 degrees

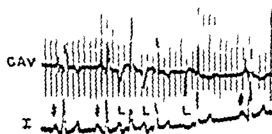


Fig 3 Left trial timula ion i subject 2 Time lines 0 1 second The first t be t re sinoatrial. With the catheter-tip lectrode in the left trium the intrinsic deflection of the itary I f ll on the descending limb of the P w i Lead I The third beat is LAPC in hich the itary P wa e demonstr tes the sudden hang in slope after the intrin ic deflection has ret rned bout halfw y to the baseline The fourth beat is LAPC i wh h the slower slope commences t the nadir of the ca itary I w The corresponding surface P es in beats th ee and f u occur near the end of the preceding T e. The fifth beat is of left atrial orig but is not premature l learly show the typical lation bet een left trial ca tary P w and surfac P f r a left trial be t. The last beat is of sinoatrial origin.

Relationship between surface and cavitary P waves An intracavitary P wave which was entirely negative and began with a rapid intrinsic deflection was the criterion for a left atrial contraction originating at the tip of the catheter After the rapid initial negative deflection there was generally a rapid partial return toward the base line which suddenly gave way to a more gradual slope and slower return to the base line The onset on the surface P wave was coincident with this sudden change in slope which marks the end of the rapid intrinsic deflection (Figs. 2-4)

P R interval The I R interval which occurred with conducted LAPCs was generally little changed However one patient demonstrated frequent *shortening* of a normal I R interval to 0 08-0 10 second this occurred in 10 LAPCs. Also another patient with an ostium primum atrial septal defect and first-degree heart block demonstrated further lengthening of the I R interval with one LAPC

Clinical observations

C se 1 The patient is 56-year-old whit oman who re-entered the hospital for n interv l evaluation of her pulmonary stat At the ge of 48 she had undergone right pper lobectomy for activ parenchymal pulmonary tuberculosis nd stenos-

ing lesion of the right main-stem bronchus. Preoperatively and immediately postoperatively the electrocardiogram demonstrated normal sinus mechanism. On the fourth postoperative day the cardiac rhythm was irregular. An electrocardiogram revealed frequent sinus pauses permitting isolated A-V nodal beats not accompanied by any P waves. On the seventh postoperative day a regular supraventricular rhythm appeared, with totally inverted P waves in Lead I and a P-R interval of 0.16 second,

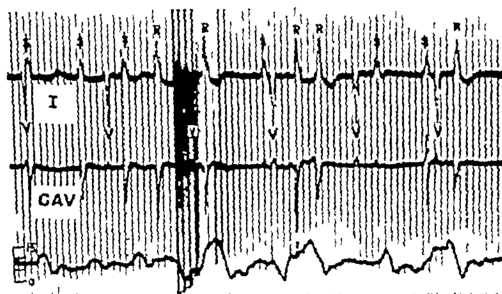


Fig. 4A. Stimulation of the *right* atrium in Subject 3. Time lines 0.1 second. Complete heart block is present with sinoatrial rate of 75 and ventricular rate of 46. The first three atrial beats are of S-A origin ($). With the catheter electrode in the high right atrium the intrinsic deflection occurs at the start of the surface P wave. Ectopic right atrial beats (*R*) show completely negative P waves in the right atrial cavity which begin with rapid deflection. The surface P wave is markedly taller than that which occurs with sinus beat. The fourth and fifth sinoatrial ($) beat occurred while the catheter tip was in a very low atrial region, accounting for the cavitary P waves appearing small, positive, and lacking intrinsic type of deflection. The bottom tracing is the atrial pressure contour in which giant a waves are seen with the second and third ectopic right atrial beats, which occur during ventricular systole as judged from the timing of the QRS complex (V).

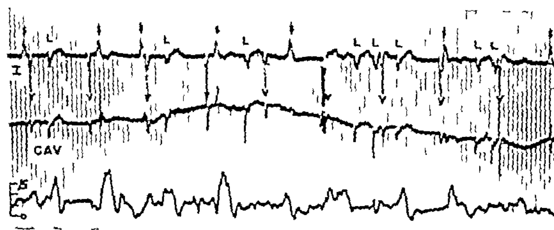


Fig. 4B. Stimulation of the *left* atrium in Subject 3. Complete heart block is present. With the catheter-tip electrode in the left atrial cavity the intrinsic deflection occurring with sinus beats ($) falls during the latter portion of the P wave in Lead I. In contrast, the intrinsic deflection within the cavity for ectopic left atrial beats (*L*) precedes the surface P wave. Both Type A and Type C morphologies of P waves are seen in Lead I with the left atrial beats. The atrial pressure contour appears below.

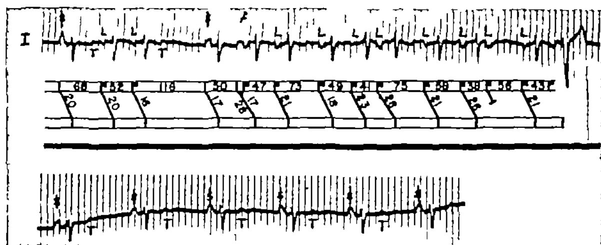


Fig. 5 Continuous record of Lead I during left atrial stimulation in Subject 5 The simultaneous cavitary and pressure tracings are omitted. Time lines 0.1 second. S, Sinoatrial beat. L, Left atrial beat. f Atrial fusion beat. The conventional line diagram applies to the upper strip time intervals are in one-hundredths of second beats arising in the left atrium are indicated by square, black flag. The morphology of T waves occurring with a supraventricular QRS can be identified after the first third, and last six QRS complexes, and is small, upright deflection. Therefore, the left atrial beat (L) which were always accompanied by negative P waves, can be identified as such, even when occurring during the preceding ST T period. Several of the morphologic types of left atrial P waves are seen. Near the end of the upper strip is a non-conducted LAPC. The last atrial beat on the upper strip was either followed by premature ventricular contraction or conducted with aberrant intraventricular conduction. Left atrial stimulation ceased at this point and was followed by sinus bradycardia. (The lower strip is continuous with the upper strip.)

and has persisted as the permanent rhythmic mechanism. The electrocardiogram remains unchanged 8 years after the onset of this rhythm (Fig. 7A). While this routine tracing was being recorded, a fortuitous A-V nodal premature contraction discharged the pacemaker and the ensuing pause allowed the less rhythmic S-A node to capture the heart for a single beat, followed by recapture by the usual pacemaker (Fig. 7B see legend).

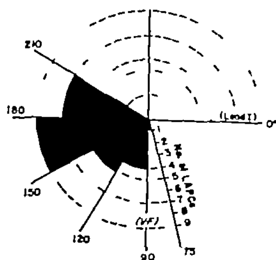


Fig. 6 Mean P vector in 26 premature left atrial contractions.

When the patient recently had mild tachycardia (112 per minute), the electrocardiogram demonstrated that a left atrial pacemaking focus was operative.

COMMENT Surgical removal of the right upper lobe, including the bronchovascular pedicle, was the source of trauma within the right side of the chest in the vicinity of the right atrium. On the fourth postoperative day depression of the sinoatrial node was demonstrated electrocardiographically It is believed that depressed rhythmicity of the sinoatrial region was permanent, permitting new supraventricular pacemaker in the left atrium to control the rhythm. This view is supported by the sequence of events commencing with an isolated atrioventricular nodal premature contraction (Fig. 7B). This sequence permitted exclusion of the atrioventricular node and the sinoatrial node as possible locations for the dominant pacemaking focus. The morphology of P waves occurring with the usual rhythmic mechanism places the pacemaker in the left rather than the right atrium.

Case 2 The patient is a 59-year-old white man who had had two episodes of acute rheumatic fever at ages 9 and 16. Two years ago he experienced the onset of typical angina pectoris, which was regularly relieved by nitroglycerin. Dyspnea and orthopnea were denied. Recently occasional wheezing occurred, and an oral diuretic produced vigorous diuresis.

At this time the blood pressure was 180/75 mm. Hg, and the pulse was regular at 95 per minute. Bilateral basilar rales were audible. The heart was enlarged. There was a harsh Grade 3 aortic sys-

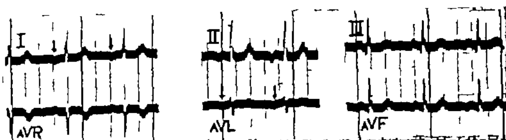


Fig. 7A Case 1. Recent routine tracing. The rate is 75, with a P R interval of 0.18 sec., and a normal QRS complex. The P wave is completely negative in Leads I and VL and biphasic in Leads, II III, and VF

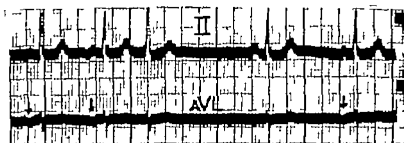


Fig 7B Simultaneous Leads II and VL recorded at same time as the tracing shown in Fig 7A. The first two beats represent the usual rhythmic mechanism. The morphology of P-QRS-T is identical with that shown in Fig 7A. The third beat is an A-V nodal premature contraction, whose QRS complex is of slightly greater amplitude and 0.02 second longer that that which occurs with the usual rhythmic mechanism. The slight increase in area of the QRS complex is accompanied by secondary decrease in T wave area, resulting from slight decrease in T-wave amplitude. After the A-V nodal premature contraction there is long pause of greater duration than simple compensatory pause. This is interpreted as indicating that the A-V nodal beat produced retrograde atrial depolarization with entry into the usual left atrial pacemaker and temporary *depression of its* rhythmicity. The long pause permitted the S-A node to capture the atria and ventricles (fourth beat), resulting in normal P-wave morphology and normal mean P vector at approximately 65°. The last (fifth) beat probably represents the return of pacemaking to its usual left atrial location.

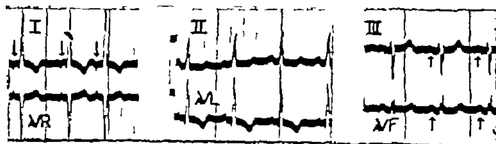


Fig. 8 Case 2. Rate 78. P R = 0.18 sec. There is large-amplitude QRS in Lead I with delayed intrinsicoid deflection and ST T changes. The left precordial leads also were indicative of left ventricular hypertrophy. The P R interval measured in Lead I is 0.06 second shorter than that measured in Leads II and III, indicating an initial isoelectric period in Lead I during early atrial depolarization, which is followed by negative P wave corresponding to the remaining portion of atrial depolarization. The pacemaker is believed to lie in the upper left atrium. A premature contraction originating from this pacemaker is seen in the third beat of the simultaneous record of Leads I and VR.



Fig. 9. Case 3. The patient's usual rhythmic mechanism is shown. There is atrial tachycardia with an atrial rate of 150, 2:1 A-V block, and a ventricular rate of 75. The conducted beats have a P-R interval = 0.16 sec. The nonconducted P waves appear at the summit of the T wave, best seen in right chest lead (not shown) but also in Leads I and V_L, where the P wave is entirely negative. Arrows indicate occurrence of P waves. Complete right bundle branch block is present.

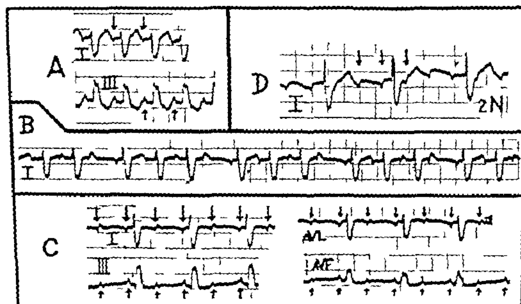


Fig. 10. Sequence of arrhythmias in Case 3. There is a regular atrial tachycardia of 150/min. in A, B, and C, and slightly faster in D. Initially 1:1 A-V conduction was present (*A*); this progressed to the Wenckebach phenomenon (*B*), 2:1 A-V block (*C*), and 3:1 A-V block (*D*). There was subsequent stabilization with the usual mechanism as shown in Fig. 9. Throughout the sequence the P waves are negative in Lead I and upright in Leads III and V_F, which is interpreted as left atrial tachycardia.

tolic murmur which radiated to the neck, and a Grade 2 aortic diastolic murmur which radiated down the left sternal border and to the apex. No mitral valvular bruits were heard.

The electrocardiogram demonstrated a horizontal QRS axis, large-amplitude QRS complexes in Lead I, V_L, and V_6, with S-T-T changes indicative of left ventricular hypertrophy. The limb lead showed the P wave in Lead I to consist of an initial isoelectric portion followed by a negative deflection. The P wave was upright in Leads II, III, and V_F, with normal P-R interval (Fig. 8, see legend). The interpretation is left atrial rhythm and left ventricular hypertrophy.

COMMENT. Of interest is the premature contraction in Leads I and V_L, showing that the left atrium is capable of the same type of prematurity as the right atrium.

Case 3. The patient is a 67-year-old woman who has had symptomatic rheumatic heart disease for the past 11 years. Presently the auscultatory findings are those of combined mitral stenosis and insufficiency. Chest x-ray films show a giant left atrium and some enlargement of the ventricles.

The patient's usual cardiac mechanism is shown in Fig. 9. Right bundle branch block is present. The atrial rate is 150, and the ventricular rate is 75. The P waves are negative in Leads I and V_L, upright in Lead II, III, and V_F, and isoelectric in Lead V_1. The mean P axis is 120 degrees. The mechanism is interpreted as left atrial tachycardia with 2:1 A-V block.

Several years ago the patient was seen for episode of tachycardia which proved to be the result of 1:1 ventricular response to her usual left atrial tachycardia (Fig. 10,*A*). During the course

treatment, varying degrees of A-V block occurred in sequence (*B, C*, and *D* of Fig. 10).

COMMENT: The patient's markedly abnormal left atrium is ample cause for the development of an irritable left atrial focus with rapid inherent rhythmicity at a rate of 150 per minute. The usual presence of 2:1 atrioventricular block permitted a comfortable ventricular rate. The series of electrocardiograms shown demonstrate that the usual varieties of atrioventricular block seen with right atrial pacemakers can also occur when the pacemaker lies in the left atrium.

Discussion

In his classic studies on the pacemaker of the heart,[14] Sir Thomas Lewis[11] established the feasibility of localizing the origin of cardiac beats in the atria. His experiments in the thoractotomized dog demonstrated that stimulation of the upper, central, and lower zones of the atria gives rise to distinctive morphologies of the atrial complex. The P waves recorded (Lead II) were upright when the upper zone was stimulated, isoelectric when the central zone was stimulated, and inverted when the lower zone was stimulated. Lead II did not reveal differences between beats which originated from corresponding zones of the two atria. The validity of these observations is still accepted, modified only by the demonstration that even when the pacemaker site is constant, changes in atrial conduction may alter the morphology of the P wave.[12]

A subsequent experimental study revealed that differentiation of left from right atrial foci was provided by Lead I. When the canine left atrium was stimulated, the atrial complex was generally negative in Lead I, whereas right atrial extrasystoles invariably resulted in an upright atrial complex in Lead I. These experimental findings have received little confirmation in clinical electrocardiography. The esophageal morphology of beats thought to originate in the left atrium was described as beginning with an intrinsic deflection in the esophageal derivation and occasionally associated with increased duration of the P wave and P-R interval.[13] Unfortunately, Lead I was not available in these records. In addition, rotation of the atria in relation to the esophagus may invalidate the accuracy of this method in attributing a given ectopic focus to either atrium. The suggestion that atrial foci may be localized by plotting P wave vectors[11] has previously lacked experimental support.

That left-to-right atrial activation would lead to inversion of the P waves in Lead I seems apparent from theoretical considerations. Levoposition of the venous atrium in cases of dextrocardia and levocardia is indeed associated with inverted P waves in Lead I.[4,5] Negative P waves in Lead I have also been observed, however, in patients with normally positioned hearts, both at rates of atrial tachycardia[6,7] and as an apparently persistent rhythm at normal rate as in our cases.

The use of the electrode catheter enabled us to produce arrhythmias which originated in a controlled left atrial focus. The surface records of these experimental rhythms bear striking resemblance to some of the clinical arrhythmias reported in the literature[4] and those illustrated from our clinical files. These observations suggest that in the absence of levoposition of the venous atrium, arrhythmias associated with inverted P waves in Lead I originate from left atrial foci. It should be noted, however, that stimulation of the left atrium does not invariably produce this atrial morphology, since at times, small or isoelectric P waves were produced. Complexes of this type were observed by Prinzmetal and his associates, but these authors did not find the more characteristic pattern of P wave inversion in Lead I, possibly because their studies were conducted in thoracotomized patients. It is unlikely that the presence of an atrial septal defect in our subjects produced P vector changes of a magnitude sufficient to influence our findings, although this possibility cannot be entirely excluded.

In clinical electrocardiography, ectopic rhythms suggestive of left atrial foci are uncommon. According to current evidence, spontaneous rhythmicity is primarily a property of specialized cardiac fibers.[14] The paucity of specialized tissue in left atrial myocardium may account for the rarity of left atrial rhythms.

Summary and conclusion

The left atrial myocardium was stimulated with a cardiac electrode catheter and ectopic beats were elicited. The mor-

phologies of P waves which occurred with 73 ectopic left atrial beats in 6 subjects were observed.

Four morphologic types of P waves were seen in Lead I; these generally consisted of an entirely negative or principally negative deflection. An isoelectric or undulating P wave was uncommon.

The electrocardiograms of 3 patients are shown which demonstrate inverted P waves in Lead I similar to those which occur with experimental left atrial beats. The possible relation of this finding to the clinical history is discussed.

The conclusion is that left atrial rhythms are clinically recognizable entities when associated with inverted P waves in Lead I provided that the venous atrium is in its usual (right) position.

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The periodic abnormalities of the temporospatial QRS vector in isolated right ventricular overwork

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The patterns of electrical potential gradients produced within and at the surface of the body by the depolarization process of the ventricles has two important characteristics which are difficult to measure while maintaining their proper relationships. First, the electrical field of potential gradients is three dimensional in its form The use of the corrected orthogonal lead system allows a spatial description of potentials. With the leads acting as a Cartesian reference frame a vector quantity in space representing an equivalent dipole of the heart potentials may be constructed with the lead potentials providing the *rectangular coordinates* of the vector head Second the cardiac potentials vary as a function of time. The complete event of ventricular activation therefore must be pictured as a series of vector quantities, each representing an increment of time from the onset to completion of the activation process. The locus of points thus produced by the vector heads produces the spatial QRS loop. An accurate system of electrocardiography then must define this locus of points in space while maintaining an accurate refer ence with time. The clinical electrocardi ogram requires that the spatial charac teristic be mentally synthesized in a best, a semiquantitative manner and th temporal relationships are lost from lea to lead The recording of plane projectio loops provides a much better spatial imag but time display still leads to inaccuracie

Our method is to represent this time varying spatial vector quantity graphi cally as a linear time function of its spheri cal coordinates. After the three vecto leads X, Y and Z are recorded simul taneously on film at a high speed, th *amplitude of each lead record* is measure at every 5-msec. interval during ventricu lar activation. These values are converte according to the equations

$$\alpha = \text{arc tan } y/x$$

$$T = \text{arc tan } \frac{z}{\sqrt{x^2 + y^2}}$$

$$\text{and SM} = \sqrt{x^2 + y^2 + z^2}$$

to polar coordinates called *alpha tilt* an

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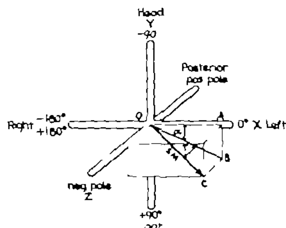


Fig. 1 The axes X Y and Z represent the recording or lead axes of the orthogonal lead system and their orientation with the torso. The polar coordinates used t describe the heart vector are the angles ($\alpha = AOB$) tilt ($T = BOC$), and the spatial magnitude (SM).

spatial magnitude which are illustrated in Fig 1 Calculation of these values by ordinary methods is a time-consuming task and has precluded their use heretofore However through the use of an electronic computer the desired data are tabulated and plotted with such ease as to make the method practicable for clinical use

Abildskov and his associates[9] tested the feasibility of this method and concluded that linear time scale plots of the vector polar coordinates presented temporal relations as clearly as conventional electrocardiograms while retaining the possible advantages of recording electric phenomena from the heart as vector quantities. He noted that wave form variations present in the spatial magnitude curve provided information not easily apparent in either the clinical electrocardiogram or plane projection Lissajous loops. The linear time scale curves of vector orientation were also of value for this highly variable characteristic could be easily qualitatively categorized into a few curve types.

The particular angles used as polar coordinates in this and our previous studies were chosen because of their familiarity in clinical electrocardiography This reference system is more easily visualized by the clinical electrocardiographer since it retains the Einthoven plane with its most commonly used angle alpha or axis and the tilt about it. This reference system also has been used by Grant,[10] Abildskov[9] Hurst and Woodson[11] and Schaefer[12] to express the orientation of the heart vector

In a previous paper[1] we reported the variations from normal of the time function of the QRS vector in a group of patients who had heart diseases which caused isolated overwork and hypertrophy of the left ventricle These abnormalities were divided into two types (1) abnormal tilt of the QRS vector in a posterior direction for variable periods during the first 40 msec of ventricular activation and (2) increase in spatial magnitude in the period from 35 to 75 msec while the QRS vector maintained a normal direction

The present paper describes the abnormal variations of the polar coordinates of the QRS vector in a group of patients with hemodynamic abnormalities which resulted in isolated overwork of the right ventricle A statistical analysis of the frequency distribution of the temperospatial QRS vector in 154 healthy adults provided the range of normal with which the present group of patients is compared[3] In this study as in the previous paper on left ventricular overwork, the patient was compared with normal subjects of his own sex and decade age group for small but clear differences in the time varying vector distribution of ventricular activation were demonstrated in normal adults as a function of their age and sex. When the age of a patient in the abnormal group exceeded the age limits of the normal group he was compared with the nearest decade age group Table I summarizes the distribution of age and sex in the normal and abnormal groups.

Method

Using the orthogonal lead system described by Helm[4] based on data published by Frank, we recorded simultaneously the scalar traces of the three leads X Y and Z on film driven at a speed of 150 mm per second The recording system including amplification and fluid-damped mirror galvanometers has a linear frequency response from 0 1 to 2,500 c.p.s. The simultaneous potential magnitudes of each lead record measured at 5-msec. intervals throughout ventricular activation are converted to

digital data on punch cards using a Benson Lehner Oscar K Model digitizing translator The Burroughs 220 electronic computer is programmed to convert these data to polar coordinates. The output prints *the values in* tabular form and plots as well each polar coordinate on a linear time base. Further details of this procedure are reported elsewhere

The present study was composed of 43 individuals who had heart disease which caused isolated overwork *of the right* ventricle The selection of cases was based on information obtained from clinical examination cardiac catheterization and heart surgery The group included 15 individuals with pure mitral stenosis and pulmonary hypertension that ranged from *35 15 to 86 46* mm Hg at rest. Eleven individuals with uncomplicated secundum atrial septal defects had pulmonic-to-systemic flow ratios of from 1 7 1 to 4.5 1 and 5 patients with secundum atrial defects had pulmonary hypertension that ranged from 47 20 to 125 54 mm Hg Two of this group had only a small bidirectional shunt across the atrial septum. The study included 4 patients who had secundum atrial septal defect and pulmonic stenosis which produced right ventricular pressures of 45 0 to 95 5 mm Hg and pulmonic-to-systemic flow ratios of 1 8 1 to 3 1 Three patients had idiopathic pulmonary hypertension 3 individuals had isolated pulmonic valvular stenosis, and one patient had a tumor obstructing the main pulmonary artery all resulting n right ventricular hypertension in the range of 65/8 to 187/8 mm Hg Finally the group included one patient with isolated tricuspid insufficiency associated with carcinoid syndrome. No patients had a clinical history of myocardial infarction and no patients were used who had a QRS duration of 120 msec or greater in order to exclude obvious intraventricular conduction abnormalities.

The diagnoses of pure mitral stenosis with pulmonary hypertension were based on the results of cardiac catheterization in 13 of the 15 patients. The other 2 patients had convincing clinical evidence of isolated mitral stenosis and pulmonary hypertension In one of these a severe mitral stenosis with a firm pulmonary artery was found by open-heart operation Twelve of the 15 patients had surgical confirmation of the anatomic diagnoses. All of the diagnoses in the other 7 patients were based on the data from cardiac catheterization and confirmed by open-heart operation in 19 patients. The mean age of the abnormal group was 40 years, with a range of 15 to 61

Results

The abnormalities which appeared to characterize overwork of the right ventricle were of three types

1 In the plot of Einthoven s alpha or the frontal plane angle there was frequently an abnormal rightward deviation of the heart vector in the period from 40 to 50 msec. after the onset of ventricular activation.

2. During the period from 35 msec. to the end of ventricular activation a tendency for abnormal anterior tilting of the heart vector occurred

3 The final abnormality frequently seen

Table I

Subjects	*Sex*	*Age groups*					*Totals*
		15-19	*20-29*	*30-39*	*40-49*	*50-61*	
Normal	Male		26	25	26	–	154
	Female	–	25	26	26	–	
Abnormal	Male	2	2	2	3	2	43
	Female	5	5	11	6	5	

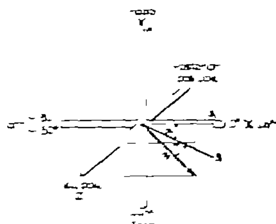


Fig. 1. The axes X, Y, and Z represent the recording or lead axes of the orthogonal lead system and their orientation with the torso. The polar coordinates used to describe the heart vector are the angles α = 165°, tilt T = 30°, and the spatial magnitude S.

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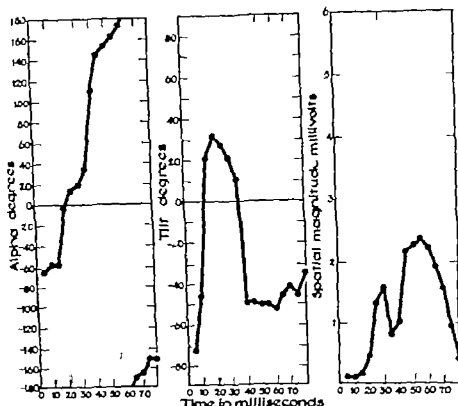


Fig. 3. The plot of findings in 20-year-old male who had primary pulmonary hypertension. The pulmonary arterial pressure was 97/48 mm. Hg, and there was no evidence of intracardiac shunt.

ations from the means, (B) one normal subject (1 per cent) had 2 points in a magnitude dip less than 1.5 standard deviation from his mean and (C) 7 normal subjects (4.5 per cent) had 1 or more points in a magnitude dip less than 1.5 standard deviation from the means.

In order to assess the frequency with which normal individuals display the combined criteria, the number of points in each record falling within the divisions of standard deviation described above were weighted as follows a value between 1.5 and 2 S.D = ½ point a value between 2 and 3 S.D = 1 point one between 3 and 4 S.D = 2 points and one greater than 4 S.D = 3 points. When all three criteria of abnormality were then considered together the normal group showed the following extremes of point totals (A) no normal subjects had a point total of 6 or greater (B) 3 (2 per cent) normal subjects had a point total of 5 (C) 9 (6 per cent normal subjects had a point total of 4 or greater and (D) 16 (10 per cent) normal subjects had a point total of 3 or more.

Allowing up to 5 per cent of normal individuals in the abnormal range, the following criteria were set to detect the presence of right ventricular overwork and hypertrophy

1 If during the period from 40 to 50 msec the heart vector deviates to the right greater than 2 standard deviations from the mean in 1 or more points, right ventricular hypertrophy is present.

2. If within the period from 35 to 75 msec. the heart vector is tilted anteriorly less than 2 standard deviations from the mean in 3 or more values, or less than 3 standard deviations in 1 or more points, right ventricular hypertrophy is present.

3 If during the period from 40 to 55 msec. a dip in spatial magnitude of the heart vector has 1 or more points less than 1.5 standard deviation from the mean right ventricular hypertrophy is present.

Table II

Disease	Number of cases	Only right axis (40-50 msec.)	Only anterior tilt (35-75 msec.)	Only dip in SM (40-55 msec.)	Right axis and anterior tilt
Mitral stenosis with pulmonary hypertension > 35 mm. Hg systolic	15	0	8	0	2
Uncomplicated atrial septal defect	11	0	2	2	0
Right ventricular obstructive diseases causing RV pressures > 35 mm. Hg systolic	7	2	0	0	5
Isolated tricuspid insufficiency	1	0	0	0	0
Atrial septal defects with right ventricular hypertension > 45 mm. Hg systolic	9	1	3	0	2
Totals	43	3 (7%)	13 (30%)	2 (5%)	9 (21%)

SM Spatial magnitude

4 If a patient shows a total of 5 or more points toward the combined tendencies of rightward deviation anterior tilt and dip in spatial magnitude then right ventricular hypertrophy is present.

The results of comparing the abnormal group against each of the above-mentioned three criteria are shown in Table II

Twelve lead electrocardiograms taken at the time of the vectorcardiograms were collected for comparison of the two methods. Based on the reports of Milnor[4] and Roman and his colleagues, three criteria were chosen as the best indication of right ventricular hypertrophy in the clinical electrocardiogram (1) frontal plane QRS axis ranging from >110° to −90° (2) R/S or R′/S ratio in V_1 > 1 and (3) R/S ratio in V_5 or V_6 < 1 The presence of any one of these three established the diagnosis.

In addition right ventricular conduction delay was diagnosed if an RSR′ complex existed in Lead V_1 with the amplitude of the R′ > 0.2 mv This height of the R′ was the upper range found by Milnor[4] in a sample of 100 normal adults. The existence of a significantly tall R′ was considered to be evidence of right ventricular overwork even in the absence of QRS prolongation. This was particularly true of the cases of mitral stenosis with pulmonary hypertension. Table III shows the results of this comparison

Discussion

The abnormalities which develop in the temperospatial QRS vector observed in this study were the result of chronic overwork of the right ventricle and presumably then were due to hypertrophy of the right ventricular portions of the myocardium but also included the effects of concomitant chamber dilatation myocardial fibrosis, and minor conduction delays. To summarize the findings of this study the heart vector in right ventricular hypertrophy deviates abnormally rightward beginning as early as 30 msec. but characteristically being in the period from 40 to 50 msec after the onset of the QRS complex. At some time during the period from 35 to 75 msec. the heart vector tilts abnormally anteriorly At about 45 msec an abrupt decrease in the magnitude of the resultant heart vector often develops for a period of 10 to 15 msec This dip in the

Right axis and dip in SM	*Anterior tilt and dip in SM*	*All abnormalities*	*Number of cases with right axis*	*Number of cases with anterior tilt*	*Number of cases with dip in SM*	*Number of cases with abnormal point total*	*Normal records*
1	2	0	3	12	3	13	2
1	3	4	5	8	10	10	0
1	0	0	7	5	1	7	0
1	0	0	1	5	1	1	0
0	1	0	3	8	1	9	0
4 (9%)	6 (14%)	4 (9%)	19 (44%)	33 (77%)	16 (37%)	40 (93%)	2 (5%)

Table III

Disease	*Number of cases*	*Conclusions from the serial 12-lead electrocardiograms*				*Orthogonal leads*	
		Right ventricular hypertrophy	*RVH and RV conduction delay*	*RV conduction delay*	*Normal*	*Abnormal*	*Normal*
Mitral stenosis with pulmonary hypertension > 35 mm. Hg systolic	15	4	4	2	5	13	2
Uncomplicated atrial septal defect	11	3	4	4	0	11	0
Atrial septal defects with right ventricular hypertension > 45 mm. Hg systolic	9	5	3	1	0	9	0
Right ventricular obstructive diseases causing RV pressures > 35 mm. Hg systolic	7	5	2	0	0	7	0
Isolated tricuspid insufficiency	1	0	0	1	0	1	0
Totals	43	18	7	12	5	41	2

spatial magnitude of the vector forces may well represent a cancellation effect of increasing potentials from the right ventricle on the remaining forces of depolarization. In cases of the most severe overwork of the right ventricle, abnormalities occur in the first 40 msec. consisting of posterior tilting of the heart vector and the subsequent development of abnormal anterior tilting

Findings in the patients of this study were compared with the criteria for left ventricular overwork published previously in order to discover any overlap of criteria. No patients in this group had increases in spatial magnitude between 35 and 75 msec while maintaining a normal direction of the heart vector although 8 patients had an increase in spatial magnitude while the vector was tilted markedly anteriorly This was generally seen in severe right ventricular overwork, for in 7 of the 8 patients the right ventricular systolic pressure was greater than 50 mm. Hg The findings in one of these patients is illustrated in Fig 3

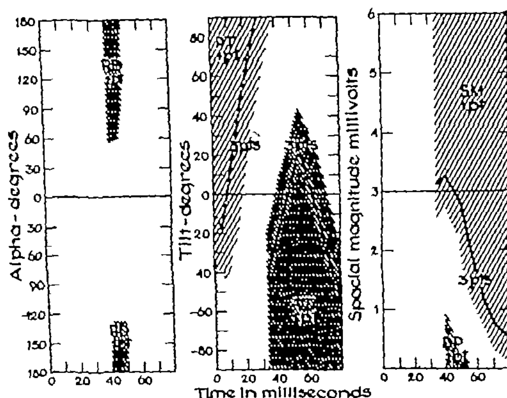
Nine patients in the present group had abnormal posterior tilting of the vector during the first 40 msec of ventricular activation. However in all of these patients the abnormality could not be confused with isolated left ventricular overwork because marked anterior tilting developed subsequently in 8 patients, and both a right axis deviation and an abnormal dip in spatial magnitude were present in the other patient.

One of the group of 46 patients with isolated left ventricular overwork was found who had one of the criteria for right ventricular hypertrophy This patient, while possessing marked abnormalities of left ventricular hypertrophy had abnormal anterior tilting which qualified with the minimum number of abnormal points. A diagram demonstrating the contrasting regions of abnormal deviation of the heart vector in right and left ventricular hypertrophy is shown in Fig 4.

A noteworthy observation is the apparent correlation of the dip in the spatial magnitude curve with the group of uncomplicated atrial septal defects. The finding occurred in 10 of the 11 patients with uncomplicated atrial septal defects, whereas it occurred only 16 times in the entire series. Also the absence of a spatial magnitude dip in a patient with an atrial septal defect was associated either with complicating pulmonary vascular disease with pulmonary hypertension or right ventricular hypertension due to a significant pulmonary stenosis for of 9 patients in this group only one had this spatial magnitude abnormality although some showed dip-like deformities which did not reach magnitudes low enough to qualify as abnormal.

The calculation of the spatial magnitude of the heart vector has thus proved to be a valuable parameter in both this study and the study of left ventricular overwork. This information is not directly available in the records of plane projection loops or scalar lead tracings. In left ventricular hypertrophy it proved to be a sensitive indicator of the increased electrical potentials. Occasionally the scalar electrocardiogram showed no voltage abnormalities, probably because the heart vector failed to parallel properly the lead vectors of the examining electrodes, so that the maximal projection of the heart vector was not recorded It may be an advantage then to derive the spatial magnitude, for this parameter is independent of the orientation of the heart vector to the orthogonal leads.

In the comparison with the conclusions drawn from the clinical electrocardiogram there were 5 cases of mitral stenosis with pulmonary hypertension in which the clinical electrocardiograms did not suggest right ventricular hypertrophy In 4 of these the present method detected abnormal anterior tilting in all and abnormal rightward deviation in one. The resting pulmonary arterial pressures at catheterization in these cases were 46/16, 35/15 60/29 and 41/18 mm Hg In one case the clinical electrocardiogram was interpreted as indicating a conduction delay in the right ventricle whereas our record demonstrated no abnormality The patient had moderate mitral stenosis with a resting pulmonary arterial pressure of 37/19 mm Hg Finally one patient with mitral stenosis and a pulmonary arterial pressure of 43/18 mm. Hg showed no abnormality in either our record or electrocardiogram



	Area	Abnormality	Time	No. Pts.
Right ventricular hypertrophy	RD	$\alpha \geq \bar{\alpha} + 2SD$	40-50	1
	AT	$T \leq \bar{T} - 2SD$ or $T \leq \bar{T} - 3SD$	35-75	3 1
	DP	$SM \leq \overline{SM} - 1.5\ SD$	40-55	1
Left ventricular hypertrophy	PT	$T \geq \bar{T} + 2SD$ or $T \geq \bar{T} + 3SD$	0-40	3 1
	SM	$SM \geq \overline{SM} + 2SD$ or $SM \geq \overline{SM} + 3SD$	35-75	3 1

Fig. 4. A diagram of the contrasting regions of abnormality seen in isolated right and isolated left ventricular hypertrophy. The stippled area represents normal distribution of the mean ± 2 standard deviations. The regions of abnormality found in right ventricular hypertrophy are shown by shading slanted to the right, and those of left ventricular hypertrophy by shading slanted to the left. Each area has been given a letter code used in the table beneath. Some areas are subdivided at 3 standard deviations, and the number of points of the plot required to meet criterion of abnormality is indicated. The table symbolically defines the criteria used for the detection of right ventricular hypertrophy and left ventricular hypertrophy.

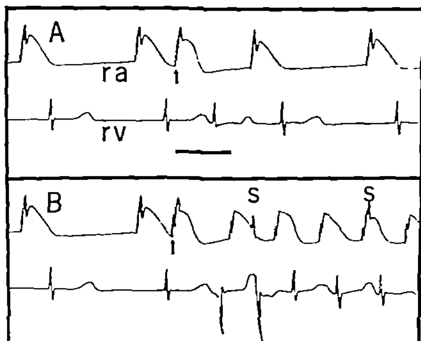


Fig. 1. *A*, Failure to initiate tachycardia, with late premature atrial excitation. Electrogram of atrium (*ra*) above, and of right ventricle (*rv*) below. At the arrow a premature atrial response follows the basic response by 185 msec. A-V conduction time, basic response, 130 msec.; premature response, 170 msec. V-V interval, 225 msec. Black bar represents 250 msec. *B*, Tachycardia initiated by earlier premature beat. A-A interval 160 msec. V-V interval 250 msec. Artefacts in atrial record (indicated by *S*) are recurrent driving stimuli falling during atrial refractory period. Note that the ventricular response to premature atrial stimulation occurs later than in *A* and that the configuration of this and the subsequent beat is altered.

right atrium and to the anterior surface of the right and left ventricles. The cardiac innervation was preserved.

Records of atrial and ventricular electrical activity were amplified and monitored on a dual-beam cathode-ray oscilloscope and were recorded on a two-channel Grass ink writing polygraph. Stimuli were delivered from a multichannel stimulator which generated precisely timed trains of pulses including driving and test stimuli as well as test stimuli triggered at will from spontaneous atrial or ventricular discharges.

Results and discussion

During the attempt to demonstrate the features of the dual A-V transmission system (temporal delay of ventricular responses, echoes, and configurational changes) it was observed that premature excitation of the rhythmically driven atrium resulted in bursts of tachycardia at a frequency of about 290 beats per minute. When this was first observed, no provision was made to interrupt the sequence of regular stimulus pulses, which usually resulted in termination of the tachycardia. So that we could study the phenomenon more carefully, the stimulation procedure was set up to permit persistence of the tachycardia, once it had been induced. This was accomplished by driving the atrium regularly at a frequency of about 2 per second, then introducing a single premature beat at a predetermined interval after one of the driving pulses, and then interrupting the stimulators at once to permit a free run of the self-sustained tachycardia. This procedure resulted in paroxysms of precisely regular tachycardia which lasted up to 60 seconds and terminated spontaneously. When the premature impulse was delivered between 120 and 180 msec. after a driving pulse, it almost invariably resulted in a paroxysm of tachycardia (Fig. 1,*B*); when the interval was increased to more than 190 msec., tachycardia never resulted (Fig. 1,*A*). Introduction of a third stimulus, between 150 and 180 msec. after the second, resulted in an exactly similar dysrhythmia

even when the second pulse was too late to succeed by itself (Fig 2,*A*)

These features of the induction mechanism are compatible with the dual transmission system previously postulated Premature impulses which resulted in tachycardia were invariable accompanied by abnormal delay of the ventricular response and were often but not always accompanied by alteration of the configuration of the ventricular response when this was recorded from the right ventricular surface near its septal margin (Fig 1,*B*)

On other occasions the heart was allowed to beat spontaneously at a frequency of about 104 beats per minute. The pacemaker was A V nodal as judged by the temporal relationship between atrial and ventricular responses (Fig 2 *C*) Atrial action potentials were amplified and delivered as discrete pulses to a scale of six counter which permitted the accurately timed delivery of one or two additional pulses to the atrium. A single premature pulse applied to the atrium failed to induce tachycardia under these circumstances but when two were delivered in sequence, a tachycardia usually resulted which was of the same frequency as that produced by one or two premature beats when the atrium was driven. Once produced the tachycardia behaved in precisely the same manner as before.

The mere production of a tachycardia by premature excitation of the atrium does not of course, establish the source and mechanism of the dysrhythmia. Since a clamp had been applied to the sinoatrial node a fairly large obstacle was available for an intra-atrial circus movement of the type described by *Rosenblueth and García Ramos*. In our experience, circus movement flutter can be readily produced about such an obstacle, but never at the slow frequency observed in the present case. For purposes of comparison, flutter was produced by a brief burst of atrial stimulation at a frequency of 25 per second. An irregular impure flutter resulted with an atrial frequency of 8 per second and a 3 2 A V block, quite out of the range of the regular tachycardia produced by

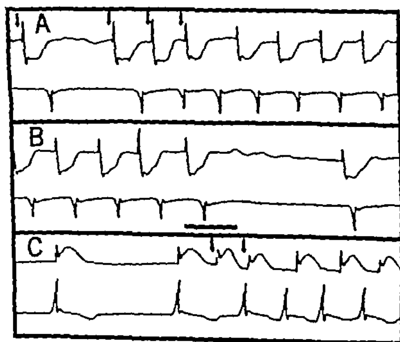


Fig. 2. *A* Initiation of tachycardia by premature atrial excitation. Atrial electrogram above, left ventricular electrogram below Arrows indicate stimuli applied to right atrial appendage. First two arrows indicate basic driving stimuli, and third and fourth indicate premature stimuli. *B* Spontaneous termination of tachycardia. Heavy black bar indicates 250 msec. Spontaneous beat at end of record is of A-V nodal origin. *C*, Initiation of tachycardia by two stimuli applied to atrium (*indicated by arrows*) during spontaneous A-V nodal rhythm.

to the junctional tissue. It is obvious that if the atrial excitable gap were less than twice this value, it would be impossible to occlude the return pathway with a single interposed atrial beat The "strategic" moment could of course, have occurred during that period when the atrium was refractory To disengage the atrium from a presumed circuit two serial stimuli were applied When this was done with appropriate timing the dysrhythmia was always abruptly terminated (Fig 4, *A B*)

It was not possible to determine whether the presumed reciprocation involved a circuit confined to the A V node, or occupied a more peripheral position in the A V conduction system. Some of the observations suggested the possibility that temporal dissociation of the right and left bundle branches might have provided a circuit For example the delay and altered configuration of early premature responses recorded from the right ventricular surface (Fig 1,*B*) were not observed when records were obtained from the left ventricle. To test the possibility that right bundle branch block accounted for the change in configuration in the right ventricular records, a sharp stylus was passed through the free wall of the right ventricle and drawn several times across the right septal surface. After the trauma, all responses recorded from the right ventricular electrodes had the same configuration as that of the premature responses of Fig 1,*B* Fig 5 illustrates the changes observed. In Fig 5,*A* responses recorded from the left ventricle near the apex (upper trace) are compared with simultaneous responses recorded from the septal margin of the right ventricle (below) These records were obtained immediately prior to the trauma to the right bundle. Right ventricular activation preceded left ventricular activation by about 5 msec. when the atrium was driven at a frequency of 2 per second. After interruption of the right bundle, the principal deflection of the right ventricular record was downward (as in premature responses of Fig 1,*B*) and the activation of the left preceded that of the right by about 20 msec. (Fig 5,*B*) Premature excitation of the atrium was still effective in inducing a paroxysm of tachycardia. The episode which was initiated as shown in Fig 5,*B* lasted for 30 seconds, after which time it was terminated by a brief burst of stimuli applied to the atrium.

Failure to prevent the paroxysms by damage to the right bundle does not prove that the reciprocation did not involve the peripheral branches of the transmission system for the possibility of bridging the gap via muscle conduction cannot be excluded nor can it be stated with certainty that all fibers of the bundle were interrupted by the trauma. However it might have been expected that the transit time should increase, thereby decreasing the frequency of the tachycardia. The frequency of the episodes induced after septal trauma was exactly the same as before.

It is impossible to state unequivocally that the tachycardia produced in this experiment was due to reciprocation and not due to repetitive discharge of a rapid pacemaker within the A V transmission system. It should be emphasized however that the manner of induction the manner of interruption and the character of the responses which initiated the disturbance were in all respects compatible with and indeed predicted by the hypothesis of a dual A V transmission system. That the dual system may have been the result of dissociation of major branches of the specialized conducting system could not be ruled out.

Summary

Premature atrial excitation was repeatedly successful in inducing paroxysms of A V nodal tachycardia in a dog The nature of the dysrhythmia and the manner of its induction and termination suggested reciprocal passage over a dual A V transmission system.

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The effect of aldosterone on electrolytes and on digital vascular reactivity to l-norepinephrine in normotensive, hypertensive, and hypotensive subjects

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In 1960 it was reported from this laboratory that glucocorticosteroids increased digital vascular reactivity to l-norepinephrine (NE) in normotensive but not in hypertensive subjects.[1] It was also reported that chlorothiazide or one of its congeners decreased such reactivity as well as blood pressure, in the hypertensive subject but that in the normotensive subject it left blood pressure unchanged and increased reactivity.[2] This seemed to implicate the sodium ion in the process of vascular responsiveness, since the major effect of the chlorothiazide group of drugs in both normotensive and hypertensive subjects is the depletion of sodium.[3] The observations also suggested that there was an optimum tissue level of this ion above and below which responsiveness to vascular stimulation seemed to be increased. In order to test the other side of the coin with reference to the effect of the sodium ion on reactivity, we undertook to measure this factor in the digit before and after administration of aldosterone.

Methods

In preliminary experiments d-aldosterone was given orally in the dosage of 0.1 mg. three times daily to 4 normotensive subjects and to 2 patients with essential hypertension. The intake of salt was controlled by having the patient on a low sodium diet (200 mg.) to which 7 Gm. of sodium chloride was added daily. No consistent change in the excretion of sodium and potassium in the urine or in the levels of serum sodium and potassium could be demonstrated. The changes in digital vascular responsiveness to NE were also inconsistent.

In the final experiments d-aldosterone-21-acetate, was given intramuscularly in sesame oil in dosage of 0.5 mg. twice daily for 3 days. For 2 days prior to the test and during the test period the patient was on a controlled daily intake of sodium chloride (7.5 Gm.) as described above. Digital vascular reactivity to NE was measured just before aldosterone was administered and at the end of the period of administra-

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Table I. Serum electrolytes before (1) and after (2) aldosterone in 12 normotensive and 10 hypertensive subjects (mEq./L.) (Mean ± SD)

Determination		Normotensive (mEq./L.)	Hypertensive (mEq./L.)
Na	(1)	142 ± 2.4	143 ± 6.4
	(2)	143 ± 6.3	146 ± 5.2
K	(1)	4.4 ± 0.71	4.4 ± 0.93
	(2)	4.6 ± 1.2	4.1 ± 0.71
CO₂	(1)	27.4 ± 2.6	26.4 ± 4.6
	(2)	26.9 ± 2.3	27.3 ± 2.3
Cl	(1)	103 ± 3.1	103 ± 2.4
	(2)	103 ± 4.0	106 ± 4.4

tion and 24-hour specimens of urine were collected before and at the height of the aldosterone effect (last day on which aldosterone was administered). Fifteen normotensive subjects and 15 patients with essential hypertension were studied. In addition ? patients with renal hypertension and 2 patients with postural hypotension were also subjected to the same procedure.

Each test of vascular reactivity before and at the height of the aldosterone effect was carried out as follows under three sets of conditions: (1) supine at rest under standardized conditions (room temperature of 26° to 29°C.) (Phase B); (2) after indirect heating for at least one-half hour with a cradle baker over the trunk until positive heat balance as manifested by profuse diaphoresis was achieved, followed by the intravenous injection of 0.8 mg. per kilogram of the sympathetic ganglion blocking agent dimethyl-1,1-diethyl piperidinium bromide (SC 1950) (Phase A); (3) infusing sufficient NE and additional SC 1950 intravenously to bring the blood pressure up to its prior level or somewhat above it (Phase C). The concentrations in the infused fluid were glucose, 50 mg. per milliliter; l-norepinephrine bitartrate, 0.0122 mg. per milliliter; and SC 1950, 0.09 mg. per milliliter. The rate of infusion was regulated with an infusion pump. Studies were not done until the blood pressure was stable.

Although the techniques have been presented in detail in previous communications,[4] some aspects of the method will be reviewed briefly. Flow in the digit was measured calorimetrically, and both diastolic and systolic arterial pressures were measured with a Gaertner capsule. These pressures were converted to mean pressure by adding one third of the pulse pressure to the diastolic pressure. A calculated venous pressure correction factor was subtracted from the mean pressure. The

Table II. Urinary electrolytes before (1) and after (2) aldosterone in 15 normotensive and 15 hypertensive subjects (Mean ± SD)

Determination		Normotensive		Hypertensive	
		mEq./L.	Total	mEq./L.	Total
Na	(1)	98 ± 40	159* ± 65	98 ± 39	121 ± 42
	(2)	6 ± 11	104 ± 40	83 ± 33	99 ± 45
K	(1)	52 ± 20	74 ± 40	70 ± 24	96 ± 36
	(2)	54 ± 19	78 ± 31	80 ± 35	95 ± 42
Cl	(1)	98 ± 18	160 ± 33	96 ± 33	121 ± 23
	(2)	98 ± 45	134 ± 51	110 ± 36	131 ± 53
Volume	(1)		1,674 ± 414		1,366 ± 41
(ml.)	(2)		1,551 ± 585		1,225 ± 477

*Standard error of the difference = 23; p < .05

Table III *Statistical analysis of digital circulatory studies 15 normotensive subjects*

	Phase	Before aldosterone Mean ± SD	After aldosterone Mean ± SD
Brachial blood pressure, systolic (mm. Hg)	A	96 ± 6	99 ± 6
	B	112 ± 13	111 ± 15
	C	135 ± 18	135 ± 17
Brachial blood pressure, diastolic (mm. Hg)	A	59 ± 6	61 ± 7
	B	65 ± 8	63 ± 7
	C	84 ± 9	83 ± 10
Digital blood pressure, systolic (mm. Hg)	A	86 ± 6	87 ± 6
	B	100 ± 15	100 ± 15
	C	123 ± 18	119 ± 18
Digital blood pressure, diastolic (mm. Hg)	A	50 ± 5	50 ± 5
	B	52 ± 15	56 ± 6
	C	72 ± 9	72 ± 12
Effective mean digital blood pressure (mm Hg)	A	52 ± 6	52 ± 5
	B	64 ± 8	63 ± 9
	C	77 ± 11	78 ± 11
Digital blood flow (cm. /cm skin/min.)	A	0 25 ± 0 048	0 27 ± 0 042
	B	0 16 ± 0 037	0 18 ± 0 077
	C	0 26 ± 0 052	0 27 ± 0 054
Radius equivalent (10^{-3} cm.)	A	3 1 ± 0 19	3 1 ± 0 16
	B	2 8 ± 0 18	2 8 ± 0 29
	C	2 9 ± 0 18	2 9 ± 0 14
Work of vasoconstriction (10^{8} ergs)	B	1 0 ± 0 58	1 3 ± 1 2
	C	0 63 ± 0 26	0 69 ± 0 30
Rate of NE infusion (μg/min.)	C	13 ± 3 9	12 ± 3 7
Work of vasoconstriction per μg NE per min. (10^{8} ergs)	C	0 049* ± 0 010	0 058* ± 0 014
Change in work of vasoconstriction per μg NE per minute (%)	C		+21** ± 30

*Standard error of the difference = 0 0044 0 05
**Standard error of the difference between hypertensive and normotensive subjects = 7.5 p 10⁻⁴
A: After vasodilatation. B Before vasodilatation. C After vasodilatation and infusion of NE.

radius equivalent of the circulation in the dilated state (Phase A) was calculated from the flow and the effective mean pressure by using Poiseuille's law A calculated length factor was considered to be constant for the digital circulation correction having been made for variation in the size of the finger tip. In both the resting and NE constricted phases of the procedure (Phases B and C) the mean digital arterial pressure was determined as indicated for Phase A. The venous pressure correction factor and the pressure axis intercept for that grade of vasoconstriction as calculated were subtracted from the mean pressure. The latter correction incorporated the factors of critical closing pressure and/or apparent viscosity as influenced by the degree of vasoconstriction The radius equivalent of the digital vessels in the constricted state was calculated from the corrected effective mean pressure and flow during vasoconstriction, by using Poiseuille's law The length factor was again assumed to

Table IV Statistical analysis of digital circulatory studies 15 subjects with essential hypertension

	Phase	Before aldosterone	After aldosterone
		Mean ± SD	Mean ± SD
Brachial blood pressure systolic (mm. Hg)	A	139 ± 28	149 ± 35
	B	181 ± 31	185 ± 32
	C	194 ± 39	216 ± 41
Brachial blood pressure, diastolic (mm. Hg)	A	89 ± 19	93 ± 21
	B	103 ± 17	102 ± 18
	C	115 ± 18	121 ± 18
Digital blood pressure, systolic (mm. Hg)	A	121 ± 23	136 ± 29
	B	164 ± 27	166 ± 25
	C	177 ± 35	196 ± 38
Digital blood pressure, diastolic (mm. Hg)	A	78 ± 17	83 ± 18
	B	92 ± 15	94 ± 16
	C	103 ± 16	110 ± 17
Effective mean digital blood pressure (mm. Hg)	A	84 ± 19	91 ± 21
	B	111 ± 17	113 ± 17
	C	120 ± 22	131 ± 23
Digital blood flow (cm.³/cm.²-skin/min.)	A	0 20 ± 0 055	0 24 ± 0 055
	B	0 12 ± 0 056	0 12 ± 0 058
	C	0 19 ± 0 061	0 19 ± 0 052
Radius equivalent (10⁻ cm.)	A	2 6 ± 0 29	2 7 ± 0 28
	B	2 3 ± 0 24	2 4 ± 0 21
	C	2 4 ± 0 25	2 4 ± 0 24
Work of vasoconstriction (10⁸ ergs)	B	2 0 ± 1 2	2 1 ± 1 4
	C	0 91 ± 0 26	1 6 ± 0 46
Rate of NE infusion (μg/min.)	C	7 2 ± 1 6	7 2 ± 1 7
Work of vasoconstriction per μg NE per minute (10⁸ ergs)	C	0 131 ± 0 040	0 233 ± 0 071
Change in work of vasoconstriction per μg NE per minute (%)	C		+90* ± 61

*Standard error of the difference = 0 021 p 10⁻⁵
**Standard error of the difference between hypertensive and normotensive subjects = 17.3 p < 10⁻⁵
A: After vasodilatation, B: Before vasodilatation, C: After vasodilatation and infusion of NE.

be unchanged From the pressures and the change in radius equivalent the force and work of vasoconstriction were estimated and from the work and infusion rate the work per microgram of NE infused per minute was calculated The formula used for calculating the work of vasoconstriction was that shown below

$$w = 197\ P_1 (r_1^3 - r_2^3) - \frac{16.1\ P^2}{Q_1} (r\ \ - r^6)$$

in which w was work in ergs P was effective mean pressure Q_1 was blood flow and r_1 was radius equivalent during vasodilatation whereas r_2 was radius equivalent during vasoconstriction. These calculations were preferred to resistance calculations which incorporate many errors in this type of study [4]

Results

It must be remembered that only the intake of sodium was controlled and that the experiments were not carried out in a metabolic ward. Although there was a tendency for serum sodium to increase after aldosterone, this increase was not statistically significant in the normotensive group and a low order of significance ($p < 0.2$) in the hypertensive group (Table I) Changes in serum potassium chlorides and carbon dioxide were also not statistically significant. There was also consider

able scatter in the results with respect to excretion of electrolytes and water in the urine (Table II) Although there was a greater mean retention of sodium after aldosterone in both groups this was statistically significant ($p < 0\ 05$) only in the normotensive group. The results with respect to the other electrolytes revealed no significant change after aldosterone in either group. There was a decreased mean excretion of water after aldosterone in both groups, but here too the scatter was such that the results could not be considered to be statistically significant.

Aldosterone produced no significant increase in digital vascular reactivity calculated as per cent change in resistance per microgram of NE per minute, in the normotensive group. In terms of work of vasoconstriction per microgram of NE per minute, mean responsiveness was slightly but significantly increased by aldosterone

Table V *Digital circulatory studies. 2 patients with renal hypertension*

	Phase	Patient 1 Before Aldosterone	Patient 1 After Aldosterone	Patient 2 Before Aldosterone	Patient 2 After Aldosterone
Brachial blood pressure (mm. Hg)	A	170/100	150/84	136/86	146/90
	B	208/108	176/94	152/90	156/80
	C	210/110	224/108	170/106	190/108
Digital blood pressure (mm. Hg)	A	152/90	140/74	120/76	130/70
	B	174/96	160/80	132/78	136/80
	C	188/98	204/98	154/96	178/96
Effective mean digital blood pressure (mm. Hg)	A	100	84	88	93
	B	119	100	96	90
	C	117	121	111	116
Digital blood flow (cm. /cm.^{2}-skin/min.)	A	0 27	0 29	0 08	0 14
	B	0 07	0 18	0	0
	C	0 26	0 29	0 09	0 15
Radius equivalent (10^{-4} cm.)	A	2 7	2 8	2 1	2 3
	B	2 2	2 6	0	0
	C	2 6	2 7	2 0	2 2
Work of vasoconstriction (10^{6} ergs)	B	3 8	1 3	Very high	Very high
	C	0 17	0 61	0 22	0 55
Rate of NE infusion (μg/min.)	C	7 7	7 7	7 9	8 6
Work of vasoconstriction per μg NE/minute (10^{6} ergs)	C	0 022	0 079	0 028	0 064
Change in work of vasoconstriction per μg NE per minute (%)	C		+259		+129

	Patient 1 mEq./L.	Patient 1 Total	Patient 1 mEq./L.	Patient 1 Total	Patient 2 mEq./L.	Patient 2 Total	Patient 2 mEq./L.	Patient 2 Total
Urine—Na	70	118	95	Not re-corded	52	68	44	84
K	25	42	24		68	88	43	82
Cl	64	108	85		58	75	80	152
Volume	1 680 ml.				1 300 ml.		1 900 ml.	
Serum—N	136		141		139		144	
K	4 1		3 5		4 6		4 6	
CO_2	27 8		29 5		30 9		28 3	
Cl	98		103		97		105	

A: After vasodilatation. B: Before vasodilatation. C: After vasodilatation and infusion of NE.

Table VI. Digital circulatory studies, 2 patients with postural hypotension

	Phase	Patient 1		Patient 2	
		Before Aldosterone	After Aldosterone	Before Aldosterone	After Aldosterone
Brachial blood pressure (mm. Hg)	A	82/69	96/60	84/52	116/66
	B	120/70	114/66	130/70	164/80
	C	150/84	132/80	194/96	210/98
Digital blood pressure (mm. Hg)	A	70/42	86/50	70/40	112/54
	B	104/60	100/54	110/58	148/68
	C	136/60	120/70	180/84	198/82
Effective mean digital blood pressure (mm. Hg)	A	39	48	43	63
	B	74	67	69	89
	C	76	72	87	105
Digital blood flow ($cm.^3/cm.^2$ skin/min.)	A	0.30	0.34	0.17	0.23
	B	0.02	0.05	0.14	0.15
	C	0.21	0.36	0.22	0.29
Radius equivalent (10^{-4} cm.)	A	3.4	3.4	2.9	2.9
	B	1.9	2.7	2.6	2.6
	C	2.9	3.2	2.7	2.8
Work of vasoconstriction (10^4 ergs)	B	7.4	3.4	1.1	1.5
	C	2.0	0.86	0.71	0.45
Rate of NE infusion (μg/min.)	C	16.3	11	6.2	6.2
Work of vasoconstriction per μg NE/minute (10^4 ergs)	C	0.123	0.078	0.115	0.073
Change in work of vasoconstriction per μg NE per minute (%)	C		−37		−37

	Patient 1				Patient 2			
	mEq./L.	Total	mEq./L.	Total	mEq./L.	Total	mEq./L.	Total
Urine—Na	64	128	Not recorded		22	24	60	74
K	38	76			40	44	62	76
Cl	67	134			55	61	74	91
Volume	500 ml.				1,100 ml.		1,225 ml.	
Serum—Na	140		152		146		144	
K	4.6		4.9		3.8		3.8	
CO_2	31.2		26.2		30.2		33.6	
Cl	100		105		101		101	

A. After vasodilatation. B. Before vasodilatation. C. After vasodilatation and infusion of NE.

($p < 0.05$) (Table III). In 3 cases it was actually decreased. Responsiveness was, however, very much increased by aldosterone from an initially high level in the patients with essential hypertension (Table IV). The increase was highly significant ($p < 10^{-4}$) in terms of work of vasoconstriction and also significant ($p < 10^{-3}$) in terms of resistance. The correlation between the change in vasoactive responsiveness and the change in the excretion or the serum concentration of sodium was poor. Vascular reactivity increased from an initially normal level in the 2 patients with renal hypertension (Table V). In the 2 patients with postural hypotension the initial high responsiveness decreased after administration of aldosterone (Table VI).

Discussion

The effects of aldosterone on electrolyte metabolism have been reported by

many workers.[7,23] Taquini and associates[24] gave desoxycorticosterone acetate to normotensive and hypertensive subjects and reported that in hypertensive patients it failed to decrease the excretion of sodium as much as in normotensive subjects. These results however were not confirmed by London and Terry[25] who found that both groups reacted equally well to this hormone. Similar experiments with respect to the effect of aldosterone in the two groups are not available.

Aldosterone increases the responsiveness of vascular smooth muscle to vasoactive substances in the hypertensive subject much more than in the normotensive subject. This contrasts with the effect of prednisone which increases responsiveness in the normotensive subject but not in the hypertensive subject. These observations are in accord with the results of direct stimulation by NE of vascular smooth muscle from normotensive animals. In such experiments, glucocorticosteroids produced more potentiation than did aldosterone.[16]

In addition the involvement of the sodium ion in the factor of vascular reactivity[2] is again suggested. If the thesis is accepted that the metabolic sodium pool[27] and the sodium content of vascular tissue is initially increased[14] in essential hypertension and if a direct or indirect effect on tissue sodium by aldosterone is postulated these observations suggest that either an increasing or a decrease in the sodium content of such tissue above or below the optimum level respectively increases its responsiveness to vasoactive substances. It is apparent also that despite the initially normal levels of responsiveness in the renal hypertensive patients[29] these levels can be increased by the administration of aldosterone. In the normotensive subject it might be presumed that the shift in sodium content produced by aldosterone remained within the optimum zone since the initial level of tissue sodium was probably lower than in the hypertensive subject.

Since there was a decrease in responsiveness in a few normotensive patients after aldosterone, and since there were only 2 cases of postural hypotension it is impossible to exclude chance alterations as an explanation of the decrease in reactivity in these cases. None of the normotensive group however exhibited high initial responsiveness. In the postural hypotensive therefore this initial high level of responsiveness could be attributed to decreased stores of NE in such patients,[30] as manifested by decreased excretion of NE[31] and of vanillylmandelic acid (VMA)[32] in the urine. To explain the decrease in responsiveness in these patients after the administration of aldosterone, an initially decreased sodium pool parallel to the decrease in NE stores would have to be postulated. Such a parallelism has been observed experimentally.[33] Bringing the sodium pool into the normal range by virtue of the retention of sodium would thus decrease responsiveness. It must be remembered that the depletion of sodium by thiazide drugs increases digital vascular responsiveness to NE in the normotensive subject.[5]

A direct effect of aldosterone as well as of chlorothiazide and its congeners on vascular function has been suggested by several groups.[34] This possibility is supported by the lack of parallelism between the electrolyte and the reactivity studies reported here. In other words a significant decrease in the excretion of sodium could be demonstrated only in the normotensive group and yet the hypertensive rather than the normotensive group revealed greatly increased vascular reactivity. In the absence, however of more precise measurements of ion concentrations in the extracellular and intracellular compartments of the tissues, especially of vascular tissue no definite conclusions with reference to the direct action of aldosterone should be drawn from these studies.

Summary

1. Aldosterone was administered intramuscularly to 15 normotensive subjects and 15 patients with essential hypertension who were on a fixed intake of sodium chloride. Two patients with renal hypertension and 2 with postural hypotension were also studied.

2. The excretion of sodium in the urine was significantly decreased in the normotensive group. The other electrolyte changes were inconclusive.

3 Digital vascular responsiveness to l norepinephrine was significantly increased from an initially high level by the aldosterone in the subjects with essential hypertension but only slightly increased in the normotensive subjects. It was also found to increase from an initially normal level in the 2 patients with renal hypertension and to decrease from an initially high level in the 2 patients with postural hypotension

4 The possible mechanisms involved in these changes are discussed

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Prevention of the cardiotoxic effect of quinidine by isoproterenol

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No other drug can reproduce the therapeutic effect of quinidine in chronic atrial fibrillation. Those offered as substitutes—procaineamide, atebrine, Banthine, phenadryl—proved efficacious only in paroxysmal forms and in cases of very recent onset. Fagarine (allocryptopine) which was used with fair results by Deulofeu and associates[4] Taquini[26] and McCawley and associates[6] was found to be severely toxic and hence unsuitable for clinical purposes by Scherf and co-workers.[23] Employment of quinidine is also limited, however, by its side effects. Embolism which follows restoration of atrial function may be averted by the prophylactic use of anticoagulants, the negative inotropic effect rendered harmless by suitable digitalis dosage or combination with Sympathol[24]; however, the danger of sudden cardiac arrest remains unchanged. It may occur even though we hold strictly to the rule that the drug is to be discontinued immediately on any significant widening of the QRS complex, as due to toxic damage of the conduction system. Control of the blood level recommended by Sokolow and others is not to be relied on either: cardiac arrest may be provoked as a hypersensitivity reaction even by small doses. The mortality caused by cardiac arrest cannot be considered to be negligible since it amounts to from 0.6 to 10.9 per cent of all treatments according to various authors.[11,27]

Similarity of quinidine syncope to Adams-Stokes attacks induced Lot and co-workers[13] to make use of ephedrine in the prevention of the former syndrome. They tell of favorable results: only one death and two cases of syncope were observed in 350 treatments. These authors also mention that still better results might be expected from isoproterenol, but they have not made use of this drug that is of the very first importance—according to the literature and our own experience—in the prevention of asystole. Complete lack of experimental data on the influence of sympathomimetic drugs on quinidine action prompted us to investigate whether the cardiotoxic effect of quinidine could be prevented by isoproterenol without affecting adversely its therapeutic efficiency.

Methods

One hundred thirty white rats which weighed between 130 and 170 grams were used for determinations of toxicity. Quinidine and isoproterenol were administered intraperitoneally. Electrocardiograms were

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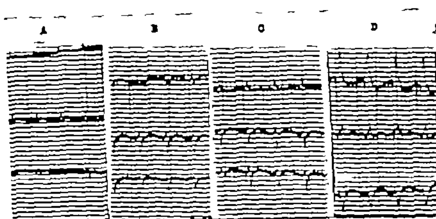


Fig. 1 Electrocardiogram of the rat prior to (*A*), and at 10 (*B*), 20 (*C*), and 30 (*D*) minutes after the injection of 100 mg. per kilogram of quinidine sulfate. The QRS interval widens by 0.03 second. (I III extremity leads. Time 0.02 to 0.1 second.)

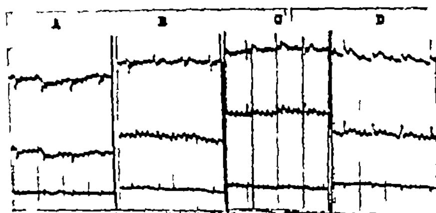


Fig. 2 ECG prior to (*A*), and at 10 (*B*), 20 (*C*) and 30 (*D*) minutes after the injection of 100 mg. per kilogram of quinidine and 5 mg. per kilogram of isoproterenol. The duration of the ventricular complex is unaltered.

registered before the injections and at 10 20 and 30 minutes thereafter (by means of a three-channel Elema Klinik apparatus at a paper speed of 90 mm per second and with crocodile clamps) The animals were in the waking state lying flat on their abdomens and immobilized with the aid of a box made for the purpose.

Excitability of the myocardium was tested by the somewhat modified method of Dawes.[3] The hearts of rabbits which weighed 1,300 to 1 600 grams were washed in oxygenated Ringer Locke solution at 30° C and the right auricle was dissected and suspended in the same solution. The preparation was fixed at the upper end whereas the lower end was attached to one pole of a fine lever—by the plate-shaped opposite end of this lever auricular contractions were communicated to a membrane-covered chamber Movements of the membrane caused changes in electrical resistance which were registered after suitable amplification by a one channel direct writing instrument The vessel which contained the suspended auricle was immersed in a water bath at a temperature of 29 to 30° C

The course of the experiment was as follows After registration of the spontaneous auricular contractions the maximal rate at which the auricle could respond without dropped beats to electrical stimulation is recorded. Then the drugs to be investigated are added to the bath and the maximal rate is measured again after

10 minutes. The preparation is washed out with pure Ringer Locke solution after each determination.

Results

Quinidine-induced myocardial damage is reflected by prolongation of the depolarization period and broadening of the QRS complex. (Lengthening of the P R interval and repolarization changes are less constant.) As shown in Table I no broadening of the QRS complex (the duration of which does not exceed 0 04 second physiologically) was observed in rats injected with 10 to

Table I Effect of intraperitoneal injection of quinidine and of isoproterenol on the electrocardiogram of rats

Quinidine (mg./Kg.)	Isoproterenol (mg./Kg.)	Number of animals	Widening of QRS complex (sec.)						Number of animals which died
			φ	0 01	0 02	0 03	0 04	0 05	
10–30	—	12	12	–	–	–	–	–	–
50	—	3	1	1	1	–	–	–	–
100	—	17	1	9	5	2	–	–	–
150	—	6	–	–	1	1	–	3	6
200	—	3	–	–	–	–	1	–	3†
100	5	19	16	1	–	–	–	–	2
100	10	9	4	3	–	1	–	1	3§
100	25	4	–	1	1	1	–	1	4§
150	5	6	–	4	–	1	–	–	3
150	7 5	8	1	3	3	1	–	–	2
150	10	3	–	1	–	1	1	–	3‡

*One animal died before the ECG was taken.
†Two animals died before the ECG was taken.
‡One animal died the following day
§Two animals died the following day

Table II Effect of quinidine and isoproterenol on spontaneous frequency and maximal rate

Number of experiments	Rate per minute in Ringer Locke bath		Bath changed to	Rate per		
				In the changed bath		
				Spontaneous		Maximal
	Spontaneous	Maximal		After 2 min.	After 5 min.	
30	151	374	Isoproterenol	207	—	415
31	184	303		184	—	332
32	184	374		237	138	415
33	111	332		207	237	332
34	151	332	(1:2,000,000)	184	—	332
42	138	303		237	184	332
64	121	415	Quinidine sulfate	—		273
67	184	415		166		332
68	184	415		184		415
70	184	332		166		207
72	151	415		151		273
73	151	312	(1 100 000)	Arrhythmia		237

30 mg per kilogram with doses of 50 mg per kilogram the first changes appeared in rats, although such changes can be induced in dogs with 10 mg per kilogram.[8] Of 3 animals, one showed a widening of 0 01 second and another of 0 02 second of the QRS duration 10 to 30 minutes after the injection none of them died One hundred milligrams per kilogram induced broadening of the ventricular complex in 16 out of 17 rats with a maximal increase of 0 03 second (Fig 1) none of these animals died. On the other hand doses which exceeded 100 mg per kilogram proved to be fatal without exception the duration of the QRS complex increased to several times its initial value, patterns of atrioventricular and bundle branch block appeared followed by a sinusoid curve and the animal died 10 to 30 minutes after the injection. The data on several animals are missing in Table I because the animals failed to survive until the first electrocardiographic control time.

The addition of 25 mg per kilogram of isoproterenol to 100 mg per kilogram of quinidine increased the toxic effects of the latter The combination proved to be lethal in every animal some died during the experiment whereas others died 24 hours later The broadening of the QRS complex exceeded that observed with quinidine alone. The addition of 10 mg per kilogram of isoproterenol caused death after a period of severe dyspnea in about 30 per cent of the animals usually on the following day in one half of the group however no electrocardiographic alteration was shown On the other hand the addition of only 5 mg per kilogram of isoproterenol to 100 mg per kilogram of quinidine gives practically full protection against prolongation of the QRS complex (Fig 2) Intraventricular conduction time increased by 0 01 second in only 1 rat out of 17 2 animals died shortly after the injection, prior to the registration of the first electrocardiogram presumably in consequence of faulty technique. The lethal effect of 150 mg per kilogram of quinidine did not seem to be affected by the addition of 10 mg per kilogram of isoproterenol nor was the electrocardiogram affected reduction of the dose to 5 mg per kilogram resulted in the survival of one half of the group and a decrease of significant degree in the prolongation of the QRS complex. The most favorable results again were given by the series with a 20 1 quinidine isoproterenol ratio the addition of 7.5

of isolated rabbit auricles at electrical stimulation

minute

After washing							
Immediately		*10 min.*		*20 min*		*30 min.*	
Spontaneous	*Max.*	*Spontaneous*	*Max.*	*Spontaneous*	*Max.*	*Spontaneous*	*Max.*
166	415	121	415	118	415	111	415
166	332	121	303	121	303	121	273
111	332	118	332	118	332	—	—
184	332	184	332	166	332	184	332
151	332	151	332	151	332	166	332
166	332	151	303	121	303	—	—
118	273	104	255	104	273	104	273
138	255	138	237	121	237	121	273
138	255	207	273	207	307	207	332
138	237	138	195	121	237	118	220
121	273	151	332	166	237	184	332
138	273	184	255	207	373	207	273

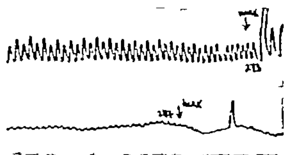


Fig. 3 Maximal rate of response of the rabbit auricle to electrical stimuli in Ringer-Locke bath (*top*) and 0 minutes after washing out of 1:100,000 quinidine solution (*bottom*).

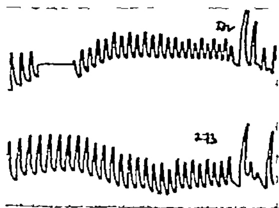


Fig. 4 Maximal rate of response of the rabbit auricle in Ringer-Locke bath (*top*) and 20 minutes after washing out of quinidine (1:100,000) and isoproterenol (1:2,000,000) solution (*bottom*).

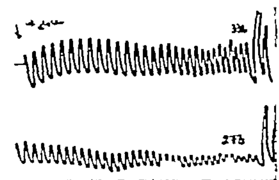


Fig. 5 Maximal response rate of the rabbit auricle in Ringer-Locke bath (*top*) and 20 minutes after washing out, first, quinidine and, thereafter isoproterenol solution (*bottom*).

mg. per kilogram of isoproterenol to 150 mg. of quinidine prevented death in three fourths of the group and the broadening of the ventricular complex was also moderate in degree.

Investigations of the reduction in the maximal rate at which isolated rabbit auricles respond to electrical stimulation were performed in 5 series. Ringer Locke solution was added to the bath in the first group (12 atria), quinidine sulfate 1:100,000 in the second group (18 atria), isoproterenol 1:2,000,000 in the third group (6 atria), and a mixture of both solutions in the fourth group (14 atria). In the fifth group 10 auricles were treated at first with quinidine, and then after being washed with isoproterenol solution each for 10 minutes.

Contractions were recorded before the bath was changed and at 2 and 5 minutes thereafter as well as immediately, 10, 20, and 30 minutes after the preparation was washed.

The course of the investigation is shown in Table II which summarizes the data of 6 experiments with quinidine and 6 with isoproterenol. The maximal rate does not vary in the latter group, nor does it diverge significantly from the controls; spontaneous frequency temporarily increased in the bath promptly returns to its initial value after washing. This factor was not affected uniformly by quinidine; the maximal rate at which the auricle follows stimulation markedly decreases under its influence in the bath as well as after washing. Therefore changes in the maximal rate are taken for comparison in further investigations. Table III shows that the maximal rate significantly decreases whether quinidine alone, combined with or followed by isoproterenol is added to the bath. The effect is marked immediately and 20 minutes after the preparation is washed; after 30 minutes, only the fourth group shows nearly significant differences in comparison to the controls. Table III also indicates that the decrease in the maximal rate of response with quinidine exceeds the changes observed on simultaneous addition of both drugs throughout the experiment but exceeds those on successive addition immediately after washing only.

Comparison of the stimulation curves indicates that the negative inotropic effect of quinidine (Fig. 3) is also prevented by simultaneous (Fig. 4) as well as successive (Fig. 5) use of isoproterenol.

Discussion

Prolongation of the effective refractory period of the heart demonstrable even on single cardiac fibers, is of foremost importance in the therapeutic effectiveness of quinidine in atrial fibrilation although the role of the slowing of the depolarization rate has been emphasized by Van Dongen [8] and Dick and associates. Lewis has already called attention to the fact however that therapeutic success may be compromised by another principal effect of the drug i.e. prolongation of conduction time. The slowing of conduction with increased preautomatic pause also plays a decisive role in the causation of cardiac arrest thus, an increase in therapeutic security through partial dissociation of both effects does not seem to be impossible theoretically Since epinephrine and norepinephrine increase conduction velocity without affecting the refractory period their orally administered derivatives would seem to be most useful for this purpose epinephrine was also found by Dreisbach to increase the fatal dose of quinine. Ephedrine Methedrine and amphetamine cause a decrease in the maximal rate at which the auricle responds to electrical stimuli whereas sympathomimetic amines in general increase conduction velocity

Of the sympathomimetic amines isoproterenol seemed to us to be the most promising It is a physiologic substance[1] used with excellent results in Adams-Stokes attacks [7] without promoting ventricular tachycardia or arrhythmia [24] and it improves the hemodynamics of the failing heart.[4,18] In our experiments the cardiotoxic effect of quinidine was significantly reduced by the addition of isoproterenol in a ratio of 1.20 The slowing of conduction which is produced by toxic but nonfatal doses of quinidine (100 mg per kilogram) is prevented almost without exception the lethality of a dose of 150 mg per kilogram is reduced from 100 to about 25 per cent with only moderate prolongation of conduction time in the surviving animals. It should be emphasized however that the dose of isoproterenol required is a critical one higher doses even increase quinidine toxicity The question whether inhibition of the effect of quinidine on conduction is to be considered as a sign of antagonism that tends to abolish the antifibrillatory effectiveness and thus diminish the therapeutic usefulness as well as the toxicity of the drug should be decided experimentally Dawes method of estimating the effect of quinidine on the reduction of the maximal rate at which the isolated rabbit auricle responds to electrical stimulation seemed to be preferable for this type of experiment to atrial fibrillation induced by electrical stimulation or acetyl

Table III Maximal rate of response to electrical stimulation after the use of quinidine or quinidine and isoproterenol

Groups	Maximal rate in Ringer-Locke bath	Percentual change in maximal rate after washing			
		Immediately	10 min.	20 min.	30 min.
I Control	384.8 ± 24.8	3.6 ± 3.1	6.2 ± 2.6	2.5 ± 2.7	6.4 ± 3.6
II Quinidine	360.5 ± 10.3	33.3 ± 3.2	35.3 ± 3.7	34.0 ± 5.8	20.3 ± 8.6
III Quinidine + isoproterenol	352.4 ± 12.3	18.8 ± 3.3	15.4 ± 3.2	15.0 ± 3.3	12.7 ± 3.4
IV Quinidine followed by isoproterenol	401.6 ± 29.6	19.9 ± 4.6	23.6 ± 6.3	22.7 ± 5.7	23.3 ± 6.6
Significance of the difference					
Groups I and II		(p > 5%)	+(p < 0.1%)	+(p < 1%)	+(p < 1%) −(p > 5%)
Groups I and III		(p > 5%)	+(p = 0.1%)	+(p = 4%)	+(p = 2%) −(p > 5%)
Groups I and IV		(p = 65%)	+(p < 0.1%)	+(p < 1%)	+(p = 1%) ±(= 5%)
Groups II and III		(p = 60%)	+(p = 0.5%)	+(p < 0.1%)	+(p = 1%) −(p = 30%)
Groups II and IV		(p > 5%)	+(p = 1.5%)	−(p = 9%)	−(p = 20%) −(p = 30%)

choline.[14,20,21] In our experiments, the maximal rate of response was invariably reduced by quinidine but unaffected by isoproterenol when these drugs were used in combination the typical effect of quinidine was maintained although it was of reduced intensity. Thus, through a combination of both drugs the therapeutic effectiveness of quinidine may be safeguarded by diminished toxicity a decrease in myocardial contractility and a lowering of arterial pressure are also warded off by isoproterenol. All this is to be considered as advantageous from the therapeutic point of view but final proof can be obtained only by extensive clinical trial. Dosages also vary with species, and doses, protective and toxic, respectively for the rat and rabbit heart may have a dissimilar effect in man. Although our clinical observations have not as yet been on a large enough scale they give evidence of favorable results.

Summary

A prolongation of conduction time induced by sublethal doses of quinidine (as shown by a broadening of the QRS interval) as well as a decrease in myocardial contractility are prevented by simultaneous administration of isoproterenol. When isoproterenol is in combination with fatal doses of quinidine, it reduces lethality from 100 to 25 per cent the dose of isoproterenol required is, however a critical one since high doses even increase quinidine toxicity Lengthening of the effective refractory period which is considered to be chiefly responsible for the therapeutic effect in auricular fibrillation is safeguarded in this combination this is demonstrated by a reduction in the maximal rate at which the isolated rabbit auricle responds to electrical stimuli. Thus, the toxicity of quinidine can be significantly reduced without any considerable curtailment of antifibrillatory effectiveness the fact that dosages may vary with species must be kept in mind when therapeutic trials are made in man

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Fig. 1. A view of the mitral valve. Note the multiple, glistening smooth amyloid vegetations, up to 0.3 cm.

in the right arm was 140/80 mm. Hg, pulse 72, respirations 20, and oral temperature 98°F. Positive physical findings were large tongue, diffuse enlargement and nodularity of the thyroid gland, increased anteroposterior diameter of the chest, with hyperresonance and scattered expiratory wheezes about the lung fields, slight cardiomegaly, and pitting edema of the soft tissue covering the scrotum, and lower extremities.

Laboratory studies revealed the hematocrit to be 37 volumes per cent, the white blood cell count was 8,500, specific gravity of the urine was 1.010 with proteinuria greater than 1,000 milligrams per cent (4 plus). Blood urea nitrogen was 89 mg. and serum creatinine 16 mg. Bromsulfophthalein retention was 8 per cent after 45 minutes. Serum sodium was 142 mEq./L., chloride 102 mEq./L., potassium 6.4 mEq./L., and carbon dioxide 18 mEq./L.

The patient left the hospital on July 11, 1961, against medical advice. He returned Aug. 5, 1961, appearing lethargic but otherwise about the same. Laboratory studies revealed urine specific gravity of 1.010, proteinuria greater than 1,000 mg. per cent (4+), blood urea nitrogen 98 mg., serum creatinine 15 mg., serum calcium 6.8 mg., and serum phosphorus 12.7 mg. Serum cholesterol was 350 mg. and serum proteins were 2.5 Gm., with 1.4 Gm. of albumin and 1.1 Gm. of globulin. Serum sodium was 140 mEq./L. The electrocardiogram demonstrated low voltage, sinus tachycardia, with first-degree heart block and right bundle branch block. Venous pressure was 9 cm. of water and arm-to-tongue circulation time was 23 seconds.

The patient remained in the hospital until his death 1 month later on Sept. 9, 1961. Therapy included digitalis for congestive heart failure and sodium lactate and ion-exchange resins for renal acidosis. Renal failure with massive albuminuria was progressive. In one 24-hour period the patient excreted 13 Gm. of albumin. The blood urea nitrogen rose to 155 mg. Prior to death he developed a gram-negative septicemia and was treated with streptomycin and Chloromycetin. Terminally, the edema increased, and the patient became more lethargic.

Necropsy. The body was that of a middle-aged white man, 160 cm. in length and weighing approximately 71 kilograms. The abdomen was distended and there was generalized edema, most marked in the lower extremities. Each *pleural cavity* and the *peritoneal cavity* contained 1,500 ml. of clear fluid. The *pericardial cavity* contained only 10 ml. of clear fluid.

The *right lung* weighed 1,200 grams. The pleural surface was smooth and glistening except in the upper part of its posterior border where fibrous adhesions were present. Cut surfaces revealed gray-red friable areas in each lobe. The *left lung* weighed 450 grams. No external abnormalities were observed. Cut surfaces revealed zones of congestion and con-



Fig. 2. A preparation of the myocardium of the interventricular septum. Note the large deposit of amyloid in the upper portion of the photomicrograph (×110).

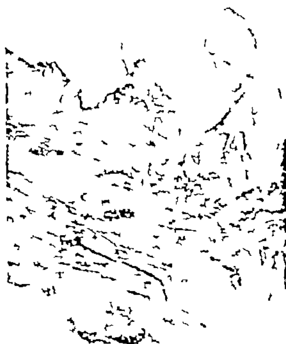


Fig. 3A. Photomicrograph rev ling one of the many amyloid errucous lesions on the mitral l v (×31).

solidation, predominantly in the pper lobe. Microscopic examination of the lungs revealed areas of bronchopneumonia and congestion. In some areas, centrilobular emphysema was observed. The small pulmonary blood vessels had an amorphous, structureless, Congo red-positive myloid substance in the wall.

The *heart* weighed 450 grams. No alterations were seen in the pericardium. The right entricle was 0.3 cm. in a erage thickness. The left entricle was 1.4 cm. in verage thickness, and no changes were seen. The *endocardium* of the ventricles was as usual. The tricuspid alve was 13.5 cm. in circumference and showed minut pale-pink nodules along the free border. The pulmonic alve was 9 cm. in circumference and showed small nodular vegetations. The mitral alve was 9 cm. in circumference and showed multiple, glistening, tan-gray smooth vegetations p to 0.3 cm. in diameter. These were locatod in the free border of the alve and on the atrial aspect of the alve (Fig. 1). The aortic valve was 7.5 cm. in circumference and revealed small verrucosities in its free border. Microscopic examination of the heart revealed areas of infiltration of amyloid in the apcal portion of the interventricular septum (Fig. 2). The blood essels were also infiltrated by amyloid material. The mitral valve showed extensive amyloid within the wall, forming nodules which were partly covered by endothelium (Figs. 3A and 3B). In some areas, deposition of fibrin was also seen, covering the verrucous lesions.

The *liver* weighed 2,260 grams. Cut surfaces revealed moderately severe passive congestion. Microscopically there was centrilobular and sinusoidal congestion. Amyloid substance was present in the walls of the portal blood essels. The *spleen* weighed 390 grams and was dull red. Cut surfaces had a dull red-brown, glossy appearance. Microscopic preparations of the spleen revealed a diffuse infiltration of amyloid which invol ed both the foll les and the pulp. The ght *adrenal gland* weighed 12 grams nd the left, 17 grams. No change was ecognized on the cut surfaces. However microscopicall both adrenal glands revealed nodular accumulations of amyloid (Fig. 4). The *ight kidney* weighed 170 gr ms, and the left, 180 grams. Their capsules were easily stripped, revealing a hyperemic cortical surface. The left kidney had an irregular red brown, depressed area in the upper pole, 2 cm. i greatest dimension. Microscopic preparations of the kidney revealed that the amyloid substance was in both the glomeruli nd the walls of the blood essels (Fig. 5). Are of chronic pyelonephritis were also seen. In the upper pole of the *left kidney* ther was an old infarct. The renal pelvis showed small hemorrhagic areas. The *thyroid* gland weighed 50 grams and was ymmetrically enlarged and rubbery. Cut surfaces were pale tan. Microscopic examination of the thyroid revealed diffuse in ol ement with amyloid substance. There was distortion and obliteration of many of the follicles although some acini still contained colloid material (Fig. 6). Sever l *mesenteric lymph nodes* were enlarged up to 2 cm. in diameter. Cut surfaces showed homogeneous tan discoloration. Microscopic preparations of these lymph nodes revealed extensi e deposits of amyloid. No alter tions were found in the remainder of the organs.



Fig. 3B. A higher magnification of the amyloid deposits on the mitral valve. Note that these lesions are covered partly by endothelium and partly by fibrin (×120).

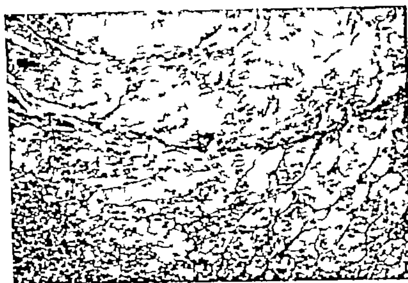


Fig. 4 Preparation of the cortex of the right adrenal gland. I the upper portion of the photomicrograph not the deposit of amyloid. Similar deposits of amyloid were found in the cortex of the left adrenal gland (×90).



Fig. 5 Photomicrograph of the renal cortex, revealing the glomeruli to be largely replaced by deposits of amyloid (×150).

Discussion

Amyloidosis has been classified into four main groups[9] (1) *generalized secondary amyloidosis* (2) *generalized primary amyloidosis* (3) *localized amyloidosis* and (4) *amyloidosis associated with neoplasms* *Generalized secondary amyloidosis* usually accompanies such chronic destructive processes as tuberculosis, rheumatoid arthritis, ulcerative colitis, chronic pyelonephritis osteomyelitis and leprosy and involves mainly parenchymatous organs, such as the spleen kidneys, liver and adrenals. In some cases it may also be present in lymph nodes pancreas, intestinal mucosa, arterioles thyroid and heart. *Generalized primary amyloidosis* has no known accompanying disease or predisposing factors and involves mesodermal structures, such as the heart tongue, larynx skeletal mus-

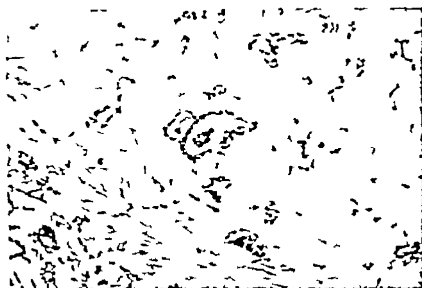


Fig. 6 Photomicrograph of the thyroid gland. The extensive deposit of amyloid almost completely obliterated the normal architecture. Only a few acini remain (X110

cle and dermis. *Localized amyloidosis* also affects mesodermal structures and is confined to one site of the body such as the heart larynx urinary bladder lungs skin anal or vaginal mucosa, salivary glands and thyroid. In the case of *amyloidosis associated with neoplasms* the lesion also is in mesodermal tissues. This type occurs in multiple myeloma Hodgkin's disease and medullary (solid) carcinoma of the thyroid gland.

The heart is often involved in primary amyloidosis and cardiac enlargement is usually seen Eliot and associates[11] in an extensive review of the medical literature of amyloidosis, found an average heart weight of 452 grams. The largest heart reported had a weight of 1,090 grams. Lindsay[9] in 1946 reviewed 43 cases of primary systemic amyloidosis of which 39 had some degree of cardiac involvement. In 32 of these cases there were clinical symptoms of heart failure and in 16 cases deposits of amyloid (predominantly microscopic) were found in the valves of the heart. A smaller number of these cases showed small visible amyloid nodules, up to 0.3 cm. in the valves of the heart. The mitral valve is most often affected but involvement of all the valves of the heart has been reported.[12] Amyloid is often present as stratified or nodular deposits in the subendocardial layer Josselson and associates in an analysis of 29 cases of amyloid localized to the heart found no verrucous valvular lesions but observed in some cases gray pink elevations, up to 0.5 mm in diameter in the atrial endocardium. Possibly the valvular vegetations produce embolic episodes as observed in cases of subacute bacterial endocarditis, Libman Sacks endocarditis, and rarely thrombotic nonbacterial (marantic) endocarditis.[13] The renal infarct seen in the present case might have been caused by an embolic amyloid fragment since some of the verrucae were not completely covered by endothelium

In this patient a diffuse generalized glomerular involvement was responsible for the clinical picture of the nephrotic syndrome. Amyloidosis is not an uncommon cause of the nephrotic syndrome It has been estimated that this complication is observed in 16 per cent of the cases of amyloidosis. Kark and associates[7] found 3 cases of amyloidosis among 46 individuals with the nephrotic syndrome one of these 3 cases was generalized primary amyloidosis. In other conditions in which there is a diffuse glomerular lesion such as acute and chronic glomerulonephritis, the nephrotic syndrome has been explained on the basis of damage to the endothelial cells, with the basement

membrane acting as a sieve which permits the passage of proteins in abnormal quantities. Others have suggested that the glomerular capillary basement membrane is not a simple sieve but a gel-like structure which is presumably built and maintained by the endothelial and epithelial cells. Damage to these cells would produce alterations in the basement membrane.[15] However the explanation of the nephrotic syndrome in amyloidosis appears to be more complex, and the proteinuria of experimental amyloidosis in mice has been related to the infiltration of the basement membrane by porous amyloid material.[14] Electron microscopy of renal biopsies in cases of renal amyloidosis has shown that the amyloid substance in focal areas penetrated and replaced the portion of the basement membrane contiguous with the epithelium. In the amyloid kidney with the nephrotic syndrome it remains to be explained whether the basement membrane is replaced by loose amyloid substance permitting increased diffusion of protein or by a true porous amyloid structure.

Summary

1 A case of generalized primary amyloidosis with congestive heart failure and nephrotic syndrome is reported. Extensive deposits of amyloid were seen in several viscera including the heart and kidneys The heart revealed verrucous valvular lesions, and the kidney showed diffuse glomerular involvement.

2 The various types of amyloidosis are discussed with particular reference to the distribution of the deposits in the heart and kidneys.

3 It is emphasized that amyloidosis should always be considered in the differential diagnosis in cases of cardiac failure and nephrotic syndrome

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Review

Bradykinin

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A number of polypeptides affect the smooth muscle of blood vessels. These include oxytocin, vasopressin,[1] angiotensin,[2] substance P (von Euler and Gaddum),[3] anaphylatoxin,[4] leucotaxine,[5] and bradykinin (plasma kinin).[7] Bradykinin is one of the least understood of these substances. Yet, despite wide gaps in knowledge concerning this substance, data obtained from animal experimentation indicate that bradykinin may hold the key to the solution of a variety of puzzling physiologic problems. Because there is little information concerning bradykinin in the clinical literature, some of the physiopharmacologic aspects of this substance are reviewed.

It is necessary to mention initially a point on nomenclature which will be discussed more fully later. It has been suggested recently that the polypeptides which are derived from plasma proteins and have the property of slow stimulation of smooth muscle and which produce vasodilatation be referred to as *plasma kinins*.[8,9] However, all of the substances studied thus far which have these properties are virtually identical to bradykinin if not the same substance. Since *bradykinin* was the name given by its discoverers (Rocha e Silva and Beraldo) to the first of the polypeptide substances to be clearly defined, and since all such substances discovered to date are similar to bradykinin, there appears to be no basis for a change in nomenclature. Accordingly, except when historical accuracy requires, we will refer to the active principle which stimulates smooth muscle and produces vasodilatation as *bradykinin*.

History of bradykinin

As early as 1928, Frey and co-workers[10-12] showed that the intravenous injection of pancreatic juice into dogs produced a hypotensive response. They called the active principle *kallikrein*. It was postulated that kallikrein was continuously released from the pancreas into the blood stream, where it circulated as an inactive complex. Reactivation of the complex would occur when conditions were proper, such as a change in blood pH. Recent work has shown that kallikrein acts on the plasma proteins to form an active polypeptide called *kallidin*, and that this substance is very closely related to bradykinin if not the same substance.[13,14]

Bradykinin was discovered by Rocha e Silva and associates[7] in 1948 during studies of the anticoagulating properties of snake venom. These workers observed that the intravenous injection of snake venom into dogs resulted in severe shock. Intravenous injection of trypsin produced the same results. By incubating pseudoglobulin prepared from ox blood with trypsin, a substance was obtained which

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had smooth-muscle-stimulating and hypotensive properties. The effect of this substance on the smooth muscle of the guinea pig ileum was a slow gradual contraction which was in contrast to the rapid contraction produced by histamine or acetylcholine. Thus, the substance was called *bradykinin* (slow to move) Rocha e Silva and collaborators postulated that bradykinin was released from an inactive precursor bradykininogen of the pseudoglobulin fraction of plasma, by snake venom or by trypsin From the physical properties of this substance, it was concluded that it was a polypeptide.[4]

Using chromatography in combination with electrophoresis, Elliott Lewis, and Horton[15] isolated pure bradykinin from crude material obtained by incubating trypsin with bovine plasma. These workers also identified the constituent amino acids of pure bradykinin [4] However the compound identified by Elliott and co-workers, an octapeptide was biologically inactive In 1960 Boissonnas and others synthesized a nonapeptide which had the same properties as natural bradykinin and which was considered to be identical or closely related to it. [1] All of the properties exhibited by crude plasma kinins could be accounted for by the single peptide bradykinin

Thus two polypeptide vasodilator substances, kallidin and bradykinin are formed by the action of certain enzymes on the plasma proteins. The activating enzymes are elaborated from many sites, including the salivary glands, pancreas, and sweat glands. However the active polypeptides formed by the action of these enzymes regardless of where they are formed, are pharmacologically identical with bradykinin. Fig 1 indicates diagrammatically the reactions leading to the formation of bradykinin.

Formation of bradykinin

Bradykinin is formed by the action of an esterolytic enzyme upon the alpha 2 globulin fraction of plasma. [20] Since esterolytic enzymes are ubiquitous in the body all tissues presumably are capable of releasing bradykinin from the plasma. However the enzyme responsible for the formation of bradykinin is found in highest concentration in glandular structures, such as the salivary glands the pancreas and the sweat glands.

A number of active substances which are released from the plasma by enzymes derived from various organs, as well as from urine (urokinase)[21] and from colostrum [24] have been described. Kallidin the most completely studied of these substances, is believed to be released from the alpha 2-globulin fraction of the plasma by the action of the enzyme kallikrein.[22,23,25,26] Kallikrein is derived from kallikreinogen a substance found in the intestines pancreas, brain submaxillary gland and serum. Kallikrein is liberated from kallikreinogen when the serum is treated with papain or acetone[26] or when serum is acidified.[27] Evidence has been presented purporting to show that the pharmacologic properties of kallikrein derived from the serum the pancreas, and the brain are different.[28] However the active product kallidin liberated from the plasma by kallikrein cannot be distinguished from bradykinin.

To summarize, many tissues in the body particularly glandular tissue possess in active precursors which when activated release an enzyme. This enzyme, in turn liberates a polypeptide from the alpha 2 globulin fraction of the plasma which has smooth muscle stimulating and hypotensive properties. This substance is called *bradykinin* Many techniques have been developed to release bradykinin forming enzymes from various organs. Differences in the rate of formation and in the pharmacologic properties of these enzymes exist. However thus far the product formed by the action of these enzymes on the plasma in all instances has been shown to be identical to bradykinin.

Pharmacology of bradykinin

At the present time bradykinin is known to have five principal activities. These are (1) stimulates (slow type) smooth muscle (2) produces vasodilatation (3) increases capillary permeability (4) causes migration of leukocytes, and (5) stimulates pain fibers.

Pure bradykinin is a nonapeptide with an amino acid sequence, as shown in Fig 2. Pure bradykinin has the same properties as natural bradykinin [7]

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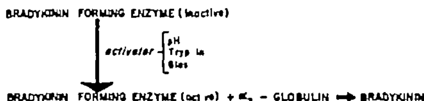


Fig. 1. Reactions leading to the formation of the polypeptide bradykinin.



Fig. 2. Amino acid sequence of the nonapeptide bradykinin.

Bradykinin is an extremely powerful stimulator of smooth muscle, being active in very low concentrations. When bradykinin is incubated with the guinea pig ileum, it produces a gradual contraction after a latent period of from 20 to 50 seconds. Bradykinin is almost as potent on a weight basis as is histamine in eliciting contractions of the guinea pig ileum and more potent than histamine on a molar basis.[17] The doses of bradykinin required to produce bronchoconstriction in the guinea pig are considerably lower than those of histamine or acetylcholine.[7] Bradykinin is almost as potent as oxytocin in causing contractions of the isolated rat uterus.

In all species of mammals thus far studied (rats, guinea pigs, rabbits, cats, and dogs), a fall in the arterial blood pressure follows the intravenous infusion of bradykinin. In man the arterial injection of as little as 1 μg of bradykinin will produce a transient fall in arterial blood pressure. However, the blood pressure response in man is quite variable, and 10 μg of bradykinin may be injected intra-arterially with essentially no change in arterial blood pressure.

The intracutaneous injection of bradykinin increases capillary permeability to circulating dyes of high molecular weight.[6,18,21] The injection of bradykinin into the cat's paw results in the formation of edema which is greater than that produced by histamine. In guinea pigs into which pontamine blue dye has been injected intravenously, an intradermal injection of bradykinin will result in an area of bluing at the site of the injection;[22] also there is a migration of leukocytes into the region of intradermal injection.

When bradykinin is brought into contact with the base of a cantharides blister, pain is produced.[23] Armstrong and his co-workers[23] have shown that plasma that had been in contact with glass will elicit pain in the base of a cantharides blister. The active substance in the plasma was called pain producing substance (PPS). Apparently, Hageman factor was necessary for the production of PPS, since the plasma from a subject with Hageman trait failed to produce pain in the base of a cantharides blister after being brought into contact with glass.[23,1] It is probable that PPS and bradykinin are identical.

Bradykinin is rapidly inactivated by peptidases present in the blood and lymph. Bradykinin-destroying enzymes also occur in the kidney and liver.[24] Phenylbutazone, salicylic acid, and amidopyrine are potent inhibitors of the bronchoconstrictive properties of bradykinin,[26,27] whereas dibenzyline, chlorpromazine, and reserpine enhance its vasodepressor effects.

Physiology of bradykinin

Within recent years the concept that various tissues are capable of controlling their blood supply independent of the central nervous system has gained in acceptance.[19] There is much evidence to suggest that bradykinin is involved in the local humoral control of blood flow to certain tissues. For example, atropine does not suppress vasodilatation in the salivary gland upon stimulation of the chorda tympani. Furthermore, the perfusate collected from the actively secreting salivary

gland elicits vasodilatation within the gland when added to the arterial blood supply of the gland.[43,44] When the perfusate from an actively secreting salivary gland is incubated with plasma, the plasma develops vasodilating and smooth-muscle-stimulating properties due to the formation of a substance which cannot be distinguished from bradykinin.[44] It appears likely that upon stimulation the salivary gland cell releases an enzyme into the interstitial fluid and blood which acts upon a plasma protein substrate to produce a vasodilating substance (bradykinin). The enzyme is released from the salivary gland whether the gland is activated by stimulation of the chorda tympani or by arterial injection of acetylcholine.[43] When the salivary gland is inactive insignificant amounts of bradykinin-forming enzyme are found in salivary gland perfusate. Thus, bradykinin is formed only in response to glandular activity at which time an augmented blood flow is required to support glandular function. Therefore, bradykinin plays an important role in the local control of blood flow to the salivary gland.

Similar observations have been made by Fox and Hilton[45] on the sweat glands of the human forearm. They found that the perfusate from the subcutaneous space of the forearm contained only small amounts of bradykinin-forming enzyme unless the trunk and legs were heated, under which conditions the activity of the perfusate increased. Fox and Hilton[45] also observed that human eccrine sweat contains a bradykinin-forming enzyme. Thus, thermal stimulation of eccrine sweat glands results in the release of increased amounts of bradykinin forming enzyme from the sweat glands, which in turn results in vasodilatation and functional hyperemia.

Bradykinin forming enzyme is also present in pancreatic juice and it is not unreasonable to consider that it plays a role in the local regulation of pancreatic blood flow. Indeed, it has been suggested that bradykinin formation is the mechanism by which all glandular tissues regulate their blood supply.[4]

Bradykinin also seems to play an important role in the regulation of the blood supply to the human finger tip. We have found that the digital vascular response to the intra-arterial injection of bradykinin is identical to that of reactive hyperemia.[38] Thus, bradykinin results in an increase in effective digital blood flow but a decrease in total digital blood flow. We have interpreted these findings to be consistent with closure of the arteriovenous anastomoses of the finger tip. Fox and associates[41] have shown that bradykinin increases the flow of blood to the human forearm.

When an intradermal bleb is raised on the human forearm with bradykinin, a marked increase in the volume of the bleb is observed. This phenomenon is associated with a slight erythema in some, but not all subjects. Usually the erythema is so slight as to be barely noticeable (Burch, G. E., Davis, W. H., and De Pasquale, N. P.: Unpublished observations). This, of course, is in marked contrast to the cutaneous vascular response produced by histamine. The increase in the volume of the bradykinin bleb is consistent with the idea that bradykinin closes arteriovenous anastomoses, since closure of these structures would be expected to result in engorgement of the capillary bed and transudation of fluid.

Recently bradykinin has been shown to increase coronary and cerebral blood flow in a variety of laboratory animals.[45,46]

On the basis of available knowledge it appears that bradykinin functions as a regulator of local blood flow. Since bradykinin is rapidly inactivated by blood and lymph, its activity is largely restricted to the tissues in which it is formed. The source of the activator of bradykinin-forming enzyme in glandular tissue is the glandular cell itself. In the finger tip the source of the activator is unknown. However, the glomus body is a possible site of origin of this substance.

Pathophysiologic significance of bradykinin

As a local humoral agent controlling blood flow in selected vascular beds, bradykinin is of immense physiologic interest and importance. However, bradykinin may also be suspected of playing a role in certain pathologic reactions.

Dermal cells contain an activator of

bradykinin forming enzyme.[47] If these cells become injured, activator (tissue kinase) is released into the interstitial fluid and bradykinin is formed. This results in vasodilatation, transudation of fluid, migration of leukocytes, and pain, all of which are well known properties of bradykinin. It was shown by Sir Thomas Lewis[41] that the first response to tissue injury was the release of H-substance (histamine) plus some other substance which Krough [9] called *H-colloid*. It seems possible that the H colloid is bradykinin. By increasing capillary permeability, the histamine released immediately upon injury may allow bradykininogen to enter the interstitial fluid, where it comes into contact with activator from the injured cells to form bradykinin. If this is so, bradykinin may be the primary mediator of the inflammatory response. The analgesic and anti-inflammatory properties of acetylsalicylic acid may well depend upon the ability of this agent to inactivate bradykinin.

The similarity of the digital vascular response to reactive hyperemia and intra-arterial injection of bradykinin suggests that bradykinin may be released by tissue ischemia. Acidification of the blood results in activation of bradykinin-forming enzyme. Since acid metabolites, such as lactic acid and carbon dioxide, accumulate during ischemic periods, the resulting acidification of the blood could possibly activate bradykinin-forming enzymes. This mechanism may explain not only the vascular responses of reactive hyperemia but also such responses as the hunting phenomenon of Sir Thomas Lewis.[14]

During anaphylactic and peptone shock the serum is altered so that it increases capillary permeability[14] and is more fibrinolytic.[13,14] It has been suggested that bradykinin is liberated during these reactions as a result of an increase in the activity of proteolytic enzymes in the blood.[9] It is conceivable that with the liberation of large amounts of bradykinin into the circulation, generalized vasodilatation and circulatory collapse would develop. However, Beraldo[14] could find no relationship between the amount of bradykinin in the blood and the development of peptone shock in dogs. Nevertheless, it is of interest that during the alarm reaction generalized vasodilatation develops and that emotion (such as preoperative stress) is capable of activating the bradykinin system.[14] Additional evidence for the liberation of bradykinin by emotion is the finding that a hypnotized subject induced to feel pain in one arm but not in the other will release bradykinin in the painful arm but not in the other.[14]

The pancreas contains large amounts of bradykinin forming enzyme, so-called pancreatic kallikrein.[13] Possibly in severe pancreatitis large amounts of this substance are released directly into the circulation, thus producing the profound circulatory collapse associated with this disease.

The pain producing properties of bradykinin may also be responsible for the symptoms seen in certain pathologic states. The intra-arterial injection of bradykinin is associated with severe pain,[14] and as already stated, bradykinin produces pain in the base of a cantharides blister. It is possible that the pain associated with the tissue injury of sunburn is due in part to the liberation of bradykinin. Furthermore, ischemic myocardial tissue may liberate bradykinin, which in turn produces the pain of angina pectoris.

Cerebrospinal fluid from normal subjects incubated with plasma does not result in the liberation of bradykinin. However, cerebrospinal fluid from patients with inflammatory diseases of the central nervous system and from patients with migraine headache and chronic schizophrenia contains bradykinin forming enzymes as well as bradykinin. The role of bradykinin in the production of migraine headache deserves particular attention.[17]

Thus, the evidence suggests that bradykinin may be implicated in a wide variety of pathologic states. A great deal more work is necessary, particularly in man, before the importance of this polypeptide in normal as well as in diseased man will be understood. However, with the recent synthesis of pure bradykinin the influence of this interesting substance on normal and abnormal physiologic responses in man will probably be more actively studied.

Problem of nomenclature

We have learned that an active polypeptide capable of stimulating smooth

muscle and producing vasodilatation is formed by the action of bradykinin forming enzyme upon the plasma proteins. The source of the bradykinin forming enzyme varies (salivary glands, pancreas, sweat glands, blood urine, etc.) The question whether the active products formed from the action of enzymes derived from different sources are identical or whether the enzymes themselves are identical is not yet answered However all the evidence to date points to the fact that the active products formed by the action of these enzymes on the plasma proteins are pharmacologically and physiologically identical, no matter what the source of the activating enzyme. G P Lewis has stated that, even if the active products do possess slightly different structures, they are probably all closely related, since they are indistinguishable by simple physicochemical and pharmacological tests. He argues that it would be cumbersome if a new name were given to the resultant polypeptide for each site and for each state in which active polypeptides are found Therefore, he suggests that all of the active products should be identified simply as plasma kinins.

Rocha e Silva [7] on the other hand has pointed out that in 1949 bradykinin was the first substance to be identified as having the following specific characteristics (1) has polypeptide-like principle, (2) produces slow type of smooth muscle stimulation (3) elicits hypotensive response in mammals, due to vasodilatation (4) is quickly destroyed after release from globulin fraction and (5) is rapidly inactivated by boiling with dilute sodium hydroxide resistant to boiling with dilute but not concentrated hydrochloric acid soluble in glacial acetic acid and 10 per cent trichloracetic acid and dialyzable through cellophane.

In 1943 Werle and co-workers[11] identified a smooth muscle stimulating and hypotensive substance released from plasma by kallikrein which they called *substance DK* However this substance which is indistinguishable from bradykinin was not fully identified until 1950 when it was renamed *kallidin* by Werle and Berek.[12] Thus, bradykinin was the first of the smooth muscle stimulating and vasodilating polypeptides to be clearly identified. All of the other smooth muscle stimulating and vasodilating polypeptides thus far identified including kallidin and PPS have chemical and pharmacologic properties which are identical to those of bradykinin Inasmuch as all of the smooth muscle stimulating and vasodilating substances are similar it would seem that on the basis of priority they should be called *bradykinin*. Substances discovered in the future that do not conform to the specifications of bradykinin can be given appropriate names as the occasion arises. If the term *plasma kinin* is to be used as a generic name for the vasoactive polypeptides, it would seem that it should also include oxytocin vasopressin angiotensin substance P etc. Rocha e Silva[7] favors retaining the name *bradykinin* on grounds that it is an indication of the pharmacologic profile of the substance described

Summary

Blood vessels are regulated primarily by the activity of the vasomotor nerves and by basal myogenic tone. However vascular beds which are involved with the metabolic functions of the organism are largely independent of the vasomotor nerves. Such vascular beds are regulated by the interaction of the basal myogenic tone and vasodilator factors from the tissues. This situation creates a "vascular reserve" which is mobilized according to the needs of the tissue by changes in the concentration of vasodilator factors. The vasodilator factor or factors have yet to be identified. It may well be that bradykinin is one of the most important of these vasodilator factors. The characteristics of this substance make it an ideal local humoral agent for the regulation of blood flow For example, it is produced in the tissues by readily available enzymes, it is a powerful vasodilator and it is rapidly inactivated by blood and lymph so that its activity is restricted to the tissues in which it is produced.

Although it is far from proved that bradykinin functions throughout the body as the local regulator of blood flow there is little doubt that it regulates blood flow at least in the salivary and sweat glands. A great deal more work is needed before the role of bradykinin in regulating blood

flow to such organs as the heart brain skin and muscle of man will be fully understood

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on obstructive cardiomyopathy and add the cases of 2 additional patients with idiopathic left ventricular hypertrophy One of our patients had frank obstructive features simulating aortic stenosis. The other suffered from a familial form of heart disease and overt left ventricular obstruction was not present although the clinical features suggested aortic stenosis. In this second patient hemodynamic studies suggested that there was also early obstruction to right ventricular outflow

Case reports

Case 1 H D 23-year-old man, entered the Cincinnati General Hospital in January 1958, complaining of exertional dyspnea, palpitation and the fear of impending death H reported neither syncope nor angina pectoris. A cardiac murmur had first been discovered during routine physical examination when he was 13 years old There was no history of rheumatic fever or of any other important illness in infancy or childhood. His mother had died of unknown causes t the age of 32. His f ther and 3 younger siblings ere thought to be in good health.

On physical examination the blood pressure as 110/70 mm. Hg the pulse rate was 80 per minute, and the temperature was 98 6°F The respiratory rate was 16 per minute. The only abnormalities were in the cardiovascular system The carotid pulses were increased. The point of maximal cardiac impulse was in the sixth intercostal space just within the anterior xillary line, and there was trong left ventricular hea At the apex loud jection systolic murmur was heard It was lso udible along the lower portion of the left sternal border and t the aortic area and was transmitted to the neck. *The second heart sound as diminished* t the aortic area. N ejection click or diastolic murmur was heard.

The electrocardiogram revealed the pattern of left entricular hypertrophy The P R interval was 0 16 second, and the QRS duration was 0.07 second Radiologic examination revealed slight cardiac enlargement hich was thought to be produced by prominence of the left entricle. The ascending aorta and aortic knob were not dilated. Calcification of the aortic alv was not demonstrated. The left entricular pressure obtained percutaneously was 190/20 mm Hg and simultaneously recorded brachial arterial pressure was 105/65 mm Hg

Because of the systolic pressure gradient of 85 mm Hg between the left entricle and he aorta diagnosis of congenital aortic stenosis was made, and i May 1960, thoracotomy was performed When the heart was exposed marked left ventricular hypertrophy as observed. A systolic thrill as felt over the pulmonary artery but there was none over the aorta. Pressures were measured in the aorta and left entricle, and t was noted tha the systolic pressure gradient of 85 mm. Hg recorded t the time of preoperativ cardiac catheterization had declined to 35 mm. Hg Since the cardiac output frequently is decreased during thoracotomy particularly w th cardiac manipulation, aortic tenosis till seemed likely Consequently *cardiac bypass and whole body perfusion* was instituted.

The aorta was opened and finger was easily inserted into the left entricle. The aortic alve ppeared to be normal in all respects and no discrete subvalvular aortic stenosis was found. The hypertrophied muscle of the outflow tract did not ppear to cause obstruction nder the conditions of cardiac bypass. The patient recovered from operation and when he was last seen 4 years later the findings were unchanged and he did not complain of any symptoms.

Case 2 R C. a 21 year-old man, was referred because heart murmur said to ha been present from birth had been found during examination for employment H was an active, thletic youth, but for several years he had noticed mild dyspnea and syncopal ttacks during exercise. For the past year he had been troubled by palpitation on exertion, hich was promptly relieved by rest. His father w under medical care for paroxysmal arrhythmia.

The patient as powerfully built young man with moderat pectus exca tum The pulse was f ll and ts petrok was rapid imparting to it jerky quality The carotid arterial pulsations were slightly exaggerated The blood pressure was 125/70 mm Hg and the pulse rat was 56 per minute. There was prominent left entricular hea e. The second heart sound as normally split and of normal tensity There as loud ejection systolic murmur maxim m t the mid-left sternal edge This murmur as less intense t the ortic area and was weakly transm tted t the neck but was quite intense t the cardiac pex There was no systolic ejection click The electrocardiogram showed an extreme pattern of left entricular hypertrophy Radiologic examination revealed slight enlargement of the heart shadow caused by *increased size of the left* entricle The ascending aorta was minimally dilated and pulsated igorously

A clinical diagnosis of congenital subaortic stenosis as made and subsequent cardiac catheterization yielded the results show in Table I.

N systolic pressure gradient across the aortic alv was found A small gradient was present between the right entricle nd the pulmonary artery but as no greater tha that seen in ma y patients w thout pulmonary stenosis. It is possible that this gradient as caused by mild obstruction of the right entricular outflow tract by the hypertrophied septum but there was *no other evidence of right* entricular hypertroph

Lef entriculography nd aortography w th Diodrast showed neither aortic stenosis nor i competence lthough the contour of the left entricular outflow tract as bnormal because of muscular h pertrophy The arterial pressure pulse curv was not characteristic of lvular aortic stenosis. These tudies excluded aortic stenosis of the usual types, nd diagnosis of idiopathic hypertrophy of the left entricle as made.

W believe that the symptoms were caused by intermittent obstruction to the outflow of the left

Table I

	P (mm Hg)		*Blood analysis*	
	Systol Diastolic	*M*	*Oxygen (ml)*	*Saturation ( )*
Aort	115 0		18 78	94 7
Left entricle	115 5 12			
Pulmonary artery	30 10	15	15 01	75 8
Right tricle	45 7			
Pulmonary edge		11		
Right t m	10 5	7		
Oxygen ptake (m)	305 8			
C rdiac index (L m 3)	4 33			

entricle that had not progressed t the point of permanent stolic left tricular obstruction.

Since this ond tion may be heritable it was decided t secure more detailed f mily history nd t examine th ther members of the family ail- ble for tudy The patient 31 year-old f ther an old hild had had n unt and an uncle who had died suddenly of heart trouble before the age of 50. An pical y tolic murmur was discovered this ma t the age of 16 subsequently he had numerous bouts of paroxysmal trial fibrillation. On physical examination in May 1961 loud systolic murmur was heard t th pex, and soft ystolic murmur t the aortic are Roentgen examination of the best showed rounding of the apex of he heart, which suggested possible left entricular h pertrophy The electrocardiogram e- ealed the Wolff I rkinson-Wh te yndrome nd premature trial beats w th aberrant conduction.

D C. 25 year of age, the patient elder sister as lso examined There was history of t t tacks of rheumatic fever in childhood, but t the time of examination there ere no ymptoms. Examination revealed rough, moderately loud, systolic murmur in the aortic area udible along the left sternal edge nd t the cardiac pex. The heart sounds t the pex nd base were normal. The best roentgenogram showed no abnormality The electrocardiogram however showed acceler ted A V conduction and cardiac rate of 48 per min te.

No abnormalities were found on clinical nd electrocardiographic examination of the patient mother younger sister and younger brother The patient chromosomes were examined (Dr Joseph Warkany) nd were found t be normal.

Daoud and associates recently reported from this center the case of 1 year-old child who under went cardiotomy after the erroneous diagnosis of congenital aortic stenosis. At autopsy the semilunar val es were normal but there was massive hypertrophy of both entricles.

Review of the literature

The clinical picture of cardiac hypertrophy in our patients resembles the familial cardiomeg ly described by Evans.[7] In 1958 Teare[2] described 8 cases of asymmetrical hypertrophy of the heart in young adults in 7 of these death occurred suddenly The hypertrophy in some of these cases was so pronounced that the ventricular cavities were unusually small.

In 195? Sir Russell Brock[1] first reported functional obstruction of the left ventricle causing subvalvular aortic stenosis. Brock initially believed muscular hypertrophy was caused by arterial hypertension but concluded in 1959[3] that the muscular hypertrophy was idiopathic

During the past 3 years a number of reports have appeared describing functional obstruction to ventricular emptying[4] [ ]

Hollman and associates[9] made a study of idiopathic cardiac hypertrophy and because of the obstructive features of the disease and because it is a primary disorder of the myocardium they employed the term obstructive cardiomyopathy In 14 of their patients there was obstruction to the outflow tract of the left ventricle but they described in addition another group with obstructive hypertrophy of the outlet of the right ventricle They reported still another group in which idiopathic cardiac hypertrophy of muscle produced obstruction to the inflow portion of the ventricles simulating mitral or tricuspid stenosis. They pointed out that asymmetrical hypertrophy of the intra ventricular septum as described by Teare may cause obstructive cardiomyopathy of either the inflow or outflow type

Except that the condition may be familial nothing is known about its cause. There is no evidence of infection and cardiomyopathy should not be confused with myocarditis. Asymmetrical hypertrophy of the septum suggests abnormal growth of muscle fibers. It is not known whether this alteration is congenital or acquired

Brachfield and Gorlin[10] have published a paper describing the various forms of what they termed functional subaortic stenosis. They emphasized the essential hemodynamic difference between this con

dition and aortic stenosis namely that the narrowing caused by muscular hypertrophy is dynamic in character occurring solely during systole. With the opening of the aortic valve at the end of isovolumetric contraction a small amount of blood passes into the aorta causing a rapid upstroke of the pulse. With continued contraction the hypertrophied septum moves into the outflow tract obstructing flow delaying total ejection and prolonging the duration of the peripheral pulse.

Such a mechanism would explain the intraventricular systolic pressure gradients reported in certain of these patients during withdrawal of the cardiac catheter from the left ventricle to the aorta since during systole there are functionally two chambers within the left ventricle Thus, the ventricular aortic systolic pressure gradient is in reality an intraventricular gradient and is caused by obstruction produced by bulging of the hypertrophied intraventricular septum into the outflow area of the left ventricle during systole This phenomenon can be visualized as a functional form of subaortic stenosis which during the early phase of systole produces little or no obstruction to the left ventricular outflow tract, but which in the latter portion of systole produces definite obstruction to outflow

This theory helps to explain the inability of the surgeon to demonstrate ventricular-aortic obstruction during cardiac bypass with elective arrest. The disorder has seldom been recognized by morbid anatomists since in the opened nonbeating heart there is no obstruction Menges and co-workers carried out careful measurements of the thickness of the free wall of the left ventricle and of the ventricular septum in autopsy specimens obtained from 20 subjects without heart disease and 50 subjects with hypertrophied hearts. They compared these measurements with those obtained from 3 patients with idiopathic cardiac hypertrophy and concluded that a ratio of 1.3 or greater between the thickness of the septum and that of the free wall of the left ventricle suggests that left ventricular obstruction had been present in life This disorder which in some respects resembles the Bernheim syndrome[18] probably occurs more frequently than has hitherto been suspected

Braunwald and co-workers[12] have reported 14 cases of idiopathic subaortic stenosis. All of the patients had systolic murmurs maximal at the apex or tricuspid area Some had reversed splitting of the second heart sound Electrocardiograms showed left ventricular hypertrophy or the Wolff Parkinson-White syndrome. With cardiac catheterization systolic pressure gradients from 40 to 185 mm. Hg were measured. In these patients the peripheral arterial pulses rose rapidly during systole. Left ventriculograms showed extreme thickening of the wall of the left ventricle which obstructed the outflow tract during the latter phase of systole.

Pare and associates[14] reported on a family in whom 87 members were examined and 30 were afflicted with a condition which seemingly was identical to muscular hypertrophy of the heart of unknown cause Autopsies in 3 of their patients demonstrated hypertrophy and fibrosis, particularly of the interventricular septum Clinical improvement followed longitudinal incision or removal of a portion of the hypertrophied muscular ring in 5 patients whereas several fatalities were reported when surgical exploration to correct valvular aortic stenosis was attempted

Diagnosis

When the disorder progresses to the stage of obstruction of the left ventricle, aortic stenosis is simulated Thus chest pain and syncope are frequently leading symptoms and the principal clinical findings are an ejection systolic murmur and left ventricular heave. The electrocardiogram and chest roentgenogram continue the deception by confirming left ventricular hypertrophy and finally catheter studies may show a systolic gradient between left ventricular and aortic pressure.

Careful attention to detail however leads one to suspect subaortic stenosis caused by diffuse muscular hypertrophy The systolic murmur is louder along the left sternal border and at the apex than at the aortic area and is usually shorter than the murmur of true aortic stenosis. It is

poorly transmitted to the neck. The characteristically slow peripheral pulses of valvular aortic stenosis are not found. The pulses are either normal or have a jerky quality caused by the rapid upstroke of the early portion of the pulse that is inscribed in the initial portion of systole before systolic obstruction develops. Quite unlike the other forms of obstruction which are produced by orifices of fixed small dimensions, the obstruction caused by muscular hypertrophy increases as left ventricular pressure rises.

In some patients two distinct peaks in the peripheral pulse can be palpated. There is general concurrence in the view of Boiteau and Allenstein that the first peak represents early ejection before significant obstruction has developed and that the delayed peak is produced by ejection of the remaining volume after the left ventricle has developed sufficient power to overcome the obstruction that develops later in systole.

Brockenbrough and associates have described the paradoxical effect that the postextrasystolic pause produces on the pulse pressure of patients with this disorder. It is well known that the arterial pressure pulse after a compensatory pause is increased in normal subjects and in patients with aortic valvular stenosis and those with discrete subvalvular aortic stenosis. In patients with subaortic stenosis caused by diffuse muscular hypertrophy the opposite occurs. During the prolonged diastole that follows a premature contraction there is increased ventricular filling. This augments ventricular contraction. The more powerful ventricular contraction increases the obstruction so that following the compensatory pause, the systolic pressure in the cavity of the left ventricle increases, whereas the systolic and pulse pressures in the arterial tree are decreased.

Electrocardiograms frequently show more than the usual pattern of left ventricular hypertrophy associated with aortic stenosis. The complexes may be larger and more bizarre, and anomalies of atrioventricular conduction such as the Wolff-Parkinson-White syndrome are not uncommon. Fluoroscopy fails to show calcification of the aortic valve and dilation of the ascending aorta is very rare. Retrograde catheterization of the left ventricle reveals that the systolic pressure gradient is not between the left ventricle and the aorta but rather within the left ventricle. The pressure pulse from the cavity of the left ventricle may show a notched upstroke.[11] Left ventriculography outlines the systolic narrowing of the outflow area of the left ventricle.[1]

Differentiation of hypertrophic muscular obstruction of the left ventricle from subaortic stenosis caused by a fibrous ring is exceedingly difficult to make and may be impossible unless cineangiocardiography demonstrates the subvalvular ring or the bulging of the intraventricular septum into the ventricular outflow tract during systole. Finally, systolic obstruction to left ventricular outflow may be demonstrated at cardiotomy. Kirklin[6] has reported that the degree of muscular hypertrophy may be estimated at operation with the finger passed into the left ventricle through the aortic valve and the thumb applied to its outer wall. A history may be obtained of similar findings or of sudden cardiac death in the family.

Cases in which idiopathic cardiac hypertrophy obstructs outflow from the right ventricle are less common. Clinical signs may suggest conventional pulmonary stenosis or a combination of aortic and pulmonary stenosis. Angiocardiograms may reveal hypertrophy of both ventricles and suggest massive enlargement of the septum. Goodwin[11] has emphasized that the lesion is apt to be progressive. In our second case the clinical features suggested aortic stenosis and the electrocardiogram was that of left ventricular hypertrophy. Nevertheless, the systolic murmur was easily heard in the pulmonary area and a systolic pressure gradient of 15 mm. Hg across the pulmonary valve was found during cardiac catheterization. These features suggest that in addition to left ventricular hypertrophy, obstruction to the outlet of the right ventricle may be developing. Clinically, obstructive cardiomyopathy involving right ventricular inflow suggests Ebstein's anomaly or mild tricuspid stenosis. Teare's series contains one patient in whom the clinical diagnosis was mitral stenosis, who at valvotomy was found

to have muscular hypertrophy obstructing left ventricular inflow

Prognosis

The condition has not been understood long enough to permit a clear statement on the prognosis. The frequency of early cardiac death in the family history and the early age at which many patients with advanced stages and manifestations of the disorder may be seen suggest that the prognosis is poor when the syndrome is fully established.

Treatment

Muscular hypertrophy of the left ventricle was first recognized as a separate entity when patients after clinical and hemodynamic investigation were operated upon for the relief of aortic stenosis. When the latter lesion was found to be absent occasional efforts were made to resect the hypertrophic muscle. The systolic pressure gradient was reduced in some and unaffected in others and several patients failed to survive the operation More encouraging results may be anticipated with increasing understanding of the lesion. Kirklin[3] obtained striking relief of obstruction in 2 cases. It is hoped that future cases will be recognized preoperatively and that operation when it is undertaken will be specifically directed toward resection of the hypertrophied muscle.

Care is necessary in the use of drugs which may by their action on the heart increase the obstruction These include agents which tend to induce frequent premature contractions and agents with a positive inotropic action on the myocardium. Strenuous exercise must be forbidden for the same reason

Summary

Two instances of idiopathic hypertrophy of the left ventricle have been reported and the recent reports which describe muscular subaortic stenosis have been summarized

Features which differentiate muscular hypertrophy from aortic stenosis include a peripheral arterial pulse with rapid upstroke and no anacrotic notch atypical location of an aortic ejection murmur and absence of aortic valvular calcification If there is a systolic pressure gradient it exists between the body of the left ventricle and its outflow tract and not across the aortic valve The functional anatomy may be revealed by left ventriculography The electrocardiogram may show in addition to left ventricular hypertrophy bizarre QRS complexes and anomalous atrioventricular conduction In some instances there is a strong familial incidence. Muscular hypertrophy may also obstruct right ventricular outflow and simulate pulmonary stenosis. When the inflow areas of the ventricles are principally involved mitral or tricuspid stenosis are simulated

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Appraisal and reappraisal of cardiac therapy

Appraisal and reappraisal of drugs used in the treatment of heart conditions

Introduction

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This section of the Journal has been established as an information service to our readers on the therapeutic value of the many drugs that are now used in the treatment of heart conditions. It was not long ago that the cardiologist had only two main drugs with which to treat patients, namely, digitalis and nitroglycerin. Today, many drugs used for various types of heart conditions are available, and the problem is to determine what drug can best be used in a particular situation.

The pharmaceutical industry has produced new drugs at an increasing rate, many of these drugs closely related to each other. Therefore it becomes necessary not only to evaluate a drug in its own right but also to compare it with several others in the same category. Such is the case of the thiazides used as oral diuretics. There are currently available nine of these compounds from which to choose. Which is the most effective? Is it the latest one to appear, or one of the others, or are they all equally effective? The answers to these questions are not easily determined, as we will point out in a subsequent issue of the Journal when the thiazides will be discussed. Other series of chemically related drugs are to be found in the cardiac glycosides used in the treatment of congestive heart failure, the nitrites used in angina pectoris, and the blocking agents used in the treatment of hypertension.

One of the greatest difficulties encountered is the inadequacy of many of the clinical reports in the literature. Simple controls are often lacking, particularly when a drug is used to relieve a symptom such as angina pectoris. As a rule, there are only a few well-designed and well executed studies of the double-blind type for any drug. In the case of angina pectoris the placebo effect may be as high as 70 per cent, so that studies not well controlled are worthless.

Another important aspect to consider is that a drug may produce a definite pharmacological action and yet be ineffective as a therapeutic agent. For instance, a drug was recently introduced for the treatment of angina pectoris. This drug, which will be discussed in another issue, produces coronary vasodilatation, increased coronary blood flow, and increased oxygenation of the coronary sinus blood, and yet several double-blind clinical studies show that it is no more effective in the treatment of angina pectoris than is a placebo. *This illustrates that it is dangerous to assume clinical therapeutic effectiveness of a drug from pharmacological data.* Whether a drug is a good therapeutic agent must be proved by controlled clinical studies.

This general introduction indicates *some* of the problems which we will encounter in bringing to you an unbiased appraisal of drugs, new and old, used in the treatment of heart conditions. We will have the help of many experts in various fields of cardiac therapy to make this section valuable to our readers.

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Evaluation of drugs used to reduce serum cholesterol

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Of the many factors thought to contribute to atherosclerosis hypercholesterolemia represents one which can be modified if not controlled in some patients. Whether such reduction is beneficial in terms of morbidity and mortality from atherosclerosis is yet to be proved

Many agents have been used to lower serum cholesterol but only those of current interest will be discussed here. The mechanisms of action include increasing synthesis and degradation of cholesterol (thyroid hormones and their derivatives) blockage of synthesis (triparanol nicotinic acid) prevention of absorption from the gastrointestinal tract (neomycin sitosterol) as well as others whose action is unclear (estrogens) Other approaches include dietary restrictions and additions (unsaturated fats)

1 Thyroxine and its analogues The inverse relationship between the degree of thyroid activity and the level of serum cholesterol led to an interest in derivatives which possess a dissociation between their cholesteropenic and calorigenic activities. These agents have no consistent effect on triglycerides. Sodium D-thyroxine, sodium D-triiodothyronine, tri-iodothyropropionic acid tri-iodothyroacetic acid and tetraiodothyroformic acid have received the greatest attention D-thyroxine has been the most extensively studied of the group its effect on total body metabolism is slight compared to its cholesteropenic activity Nevertheless it shares with all thyroid derivatives the possibility of aggravating angina in susceptible individuals, even in the absence of an increase in total body metabolism Recent animal work indicates that the levo and the dextro isomers of both thyroid hormones, as well as the propionic and acetic acid analogues, exert greater stimulatory effect on the metabolism of heart muscle than on the diaphragm liver or kidney providing some explanation why these drugs cause angina in patients with coronary artery disease. Patients without clinical heart disease do not develop symptoms with D-thyroxine. Less commonly patients on anticoagulants have been reported to require less of their anticoagulant while on D-thyroxine.

2 Triparanol This potent agent blocks the conversion of desmosterol to cholesterol at the last stage before the completion of the cholesterol molecule. The result is the accumulation of desmosterol, which has been found within the atherosclerotic lesions. The serious side effects in some patients, including ichthyosis, cataracts depilation and diminished adrenal responsiveness, have caused the withdrawal of this agent from clinical use.

3 Nicotinic acid Large doses (up to 6 Gm daily) of nicotinic acid (but not niacinamide) have reduced serum cholesterol and have produced an effect on the beta lipoproteins and total fatty acids.

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Although the mechanism of action has been studied intensively there is still no general agreement Recently it has been said that nicotinic acid interferes with the biosynthesis of cholesterol Side effects are mostly minor including gastrointestinal effects, pruritus, and flushing but major effects, such as impairment of liver function decreased tolerance to glucose, and frank diabetes mellitus, have been reported Fortunately these are reversible on discontinuance of the drug

4 *Sitosterol* This plant sterol is absorbed to a limited extent from the intestinal tract, competing for absorption with endogenous and exogenous cholesterol Its effect is so variable that there is very little interest in this substance at present.

5 *Neomycin* In large dosages (4 Gm or more) this antibiotic induces a malabsorption syndrome not corrected by a gluten free diet or corticosteroids In smaller dosage (0.5 to 2 Gm daily) it has been used to lower serum cholesterol probably effecting a reduction in intestinal flora which normally participate in the conversion of cholesterol into bile acids.

6 *Estrogens* A protective influence of the female sex hormones has been considered to be one reason for the relative freedom of the premenopausal woman from atherosclerosis. The administration of active hormone principles to the postmenopausal woman has multiple benefits, including those on bone metabolism tissue aging and hypercholesterolemia. When used in the male estrogen dosage must be low enough to avo d feminizing effects. In some recent well publicized studies, Estinyl was reported to give no protective effect from morbidity in atherosclerotic patients while lowering the serum cholesterol. On the other hand conjugated estrogens (Premarin) n dosages short of those which produce undesirable feminizing effects did offer improvement in morbid ty in patients who had had previous myocardial farctions, and yet this same regimen caused l ttle lipid-lowering effects.

7 *Heparin* Parenteral administration of heparin activates a lipoprotein lipase (clearing factor) Recently the long term intermittent administration of heparin has been reported to have resulted in a decrease in morbid ty and mortality in a group of patients who had sustained myocardial infarction. There is as yet no confirmation from other investigators. No beneficial lipid effects were noted and none could be anticipated from such biweekly therapy Sublingual heparin exerts no effect on serum cholesterol

8 *Diet* That quantity and quality of dietary fats influence the level of serum cholesterol is generally accepted but many studies have not been free of bias. The mode of feeding the same diet can exert a profound influence In some animal studies the same diet when given as a continuous feeding in animals resulted in only one fourth the cholesterol level as when given intermittently such as in "meals. The mere inclusion of unsaturated fats in the diet while offering some slight benefit, is more successful if all animal fat is excluded. A diet that is rich in polyunsaturated fatty acids provides increased excretion of fecal bile acids and neutral sterols. Such a diet, however is apt to be unpalatable and unacceptable to the patient.

Summary

The lowering of serum cholesterol will be fully justified only when some beneficial effect upon atherosclerosis can be proved in the meantime, we may act upon those inferences drawn from our present knowledge. The inherent variability and spontaneous fluctuation of the level of serum cholesterol especially in the hypercholesterolemic patient, should be kept in mind especially in the evaluation of new drugs. It is influenced by season stress and placebo and no change of less than 50 mg per cent and probably 100 mg per cent should be considered to be significant. Many studies have not been free of bias, and their results are open to question Furthermore the differences in methods of measuring cholesterol as well as the difficulty in reproducing results serve to complicate the comparison of data.

The ideal agent has not yet been found Inhibitors of biosynthesis are fraught with at least the theoretical danger of interference with li er or adrenal function Sequestration or interference with absorption may induce malabsorption alter intestinal flora—all for a rather m nor contribution by ingested cholesterol since most

cholesterol is formed from simple amino acid precursors in the liver. This may also serve to explain the limited benefit which accrues from dietary manipulation. A desirable cholesterol lowering agent might be one which could mobilize cholesterol and fatty acids and excrete them as harmless by products.

Annotations

Reoperation for mitral stenosis

In series of 264 survivors of mitral al otomy who ere followed from 5 to 11 years, the diagnosis of restenosis was made   84 and was confirmed   operation in 80. The incidence rose from 5 per cent at 5 years to 60 per cent in the small umber (2f who were followed for 9 years. Before he first operation the 80 patients w th re-tenosi did not differ from the others in regard t age trial fibrillation, heart size, calcification of the alv mitral incompetence, or associated aortic alvular di-e se Subsequent fibrillation, carditis, or mitral n-competence did not contribu   significantly   deterioration between operations

\ close relationship was pparent between restenosis and incompleteness of the first al otomy (Table I) or alvular sclerosis recorded t the first operation. This was an unexpected finding. It is clear that patients with an imperfect valvotomy or sclerotic al   ma remain well for more than 5 ear and also hat good al ot my and supple alv do not ensure that early restenosis will no occur The tendency   restenosis ma be related t individual ariation in re-ponse   the rheumatic process or to the trauma of al otom   but there is no evidence that t is due t reactiv t on of heumatism

The interval between the perations aried from 2 t 10 year with   erage of 7 years The de ision to perate gain was f rtified in some cases by the record that the first operation had been in-omplet   so tha   whether restenosis had occurred or not, there was some possibility of improving the tate of the   l e. I more han half stenosis   as great as or grea er than, it had been on the fir t occasion At the second opera on   better alotomy w   of en achieved Table II) and this was t ributed o greater experienc   nd be se of the tra sventricula dila or

Table I Extent of valvotomy in 80 patient who did and 184 who did not equire a second operation

	Patients requiring second valvotomy	*Patients not equiring second alvotomy*	*Total group*
Cusps completely separated anteriorly and posteriorly	23 (36)	41 (64)	64
Cusps completely separated anteriorly or posteriorly	36 (25	111 (75)	147
Cusps not completely separa ed anteriorly or posteriorly	21 (40)	32 (60	53
Total	80	184	264

Table II Extent of valvotomy at first and second operat ons

	Number	*Cusps ompletely separated nteriorly nd posteriorly*	*C s completely separated anteriorly or posteriorly*	*C s not completely separated anteriorly posteriorly*
First operation	80	23 (29)	36 (45)	21 (26)
Second operation	80	33 (41)	4 (52)	5 ( )

The per l mort li w 2 4 pc nt Fr mat mlt l ompeter (f w 8 pc t) nd y term embol m (6 ses 8 pc ent were not ig t l mon f q e h f er th first per t The pr l t m d m t mut l ne mpe w j l ed li be urrenc d or mt se d m m A pres tion g t this mpl t m nsidered import t l emov ll pressu re f m he lilu ir mmediat l the res nc d the l l l t g w y ad t w he lilat ag t of the ps ha not l en emplet l w p ted either t eul or posteriorl

The result d the sec ond oper tion ha been bserved ov r period from 6 month to 8 y rs. For ma y the follow p lat rs l has been short. It seems lik ly ho ever that bec se d the prog ess of heumatic heart dise se the long term result will be less g ood than after the first oper tion

l Lega F R C.S
C P Leather M B F R F P S.C
M R.C P E.
R S D Turne O.B.E. M I M.D
F R C.P F R C P.E.
Dept f Thoracic Surg y The R yal
I firma y Ed burgh Scotl d

Normal hemoglobin level and coronary heart disease

A re iew of avail ilable epidem olog l nd lin l da indic tes that what is presentl epted by m y ph icia normal hemoglobi level may ha et olog l sig fic nc in he st d d coronary he rt dise se ert susceptible individual

The stim lu for th review was the observ tion that l group d Jewish nd l lia patients mong whom coronary heart d se se w ery common he hemoglobi level were usually bov 14 Gm er ent I contra t group of Negro nd Puert R patient in the same age group coronary heart disease w not common nd the hemoglobin levels were sually between 10 nd 14 Gm. per cent

A review of the literature revealed that this observation—that persons suff ring from coronary heart disease often ha higher hemoglobi level tha person w hout coronary heart disease—was not original[1] but, perhaps bec se of the influence of study that spe fic lly rejected the lidity of this observation this sociation has not bee thought worthy of comment much less cceptance standard America cardiology textbooks. How ever in iew of recent work which supports the alidity of this observation, comment on other data is believed to be warra t d

First certain cli ical correlations ca be recalled For example, coronary heart disease was ery rare in patients with untreated pernicious nemia and is ery common persons with polycythemia era in addition it is generally accepted that persons who die w th certain chronic wasting diseases—such as t berculosis portal cirrhosis, nd certain forms of cancer[14]—that re accompanied by low hemoglobin levels often ha e less coronary heart disease than do persons of comparable age race, and sex who die suddenly due t ccidents.

Second, epidemiological data indicate that in those areas of the world in which anemia is public health problem, the rates of coronary heart disease re low. In contr t in those areas of the world such the United States, in which anemia is not a major public health problem the r tes of oronary he rt dise se are high Furthermore the lower hemoglobin lev l of premenopausal America women ompared to those of American men in the same age group may well be reason for the generally accepted sex ariations in coronary heart disease

I the liter ture[8] these arying rates of coronary heart disease ha frequently been associated w th umerous factors but pparently not ith the hemoglobin lev ls of these populations.

Accordingly one may reflect whether high hemoglobi level is merely an sociation w th one of the presently considered probable etiological factor i coronary heart disease e.g in certain nemias, the hemoglobin levels ary directly w th certain serum lipid levels[10] whether high hemoglobi level itself is n etiological factor rather tha the f t i coronary hea t dise se or whether it is merely reflection of an unknown tiological factor in coronary heart disease

It should he noted that this comment ha been arbitrarily limited t the hemoglobin level as matter of con enience therefore there is no discussion of whether the hematocrit the number of red blood cells, or some other red blood cell lue would offer more valid standard I addition, no theory is being submitted t this time t explain the mechanism by which increase in the hemoglobin level can cause coronary heart disease in certain susceptible persons.

Wintrobe[7] gives the normal hemoglobin lev ls for d lt men as 16 plus or minus 2 Gm. per cent and for dult women 14 plus or minus 2 Gm per cent. H then goes on t state that the ange of normal represent lmost the extremes of the observed variations (93 per cent or more) and therefore the blood counts of most healthy adult men and women should fall within these limits. It

ppears, therefore that the erage hemoglobin evels of pparently healthy adult ha been ac cepted by many physicians as the normal hemoglobin levels, and that levels below these a erag levels may be considered as anemic levels, and therefore often undesirable

It may be however that just as epidemiological and clinical studies has indicated that the recommended normal weight for an dult American should be below the erage weight in order to reduce the probability of morbidity and mortality from several diseases,[14] so further study of this problem may indicate that the normal hemoglobin level for certain susceptible indi iduals should be below the verage level.

I wish t emphasize trongly that I do not ad vocate, on the basis of the foregoing discussion, that the presently accepted normal hemoglobin levels be discarded in fa or of low normal or nemic levels, or that physicians routinely recommend diet that may lower the hemoglobin level, or tha phlebotomies become routine therapy for the prevention and treatment of coronary heart disease. Any valid recommendation must wait further study and reflection on this subject.

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Isocarboxazid (Marplan) in the treatment of angina pectoris

E aluation of the effect of any drug in symptomatic condition such as ngina pectoris is xtremely difficult. The frequency and severity of the pain aries spontaneously during the course of he illness and many factors, such as emotions and the patient temperament, are of great importance. Previous experiences has shown that in 35 t 40 per ent of the cases some benefit ma be obtained from ad ministration of placebo. Therefore one migh expect ny drug which diminishes anxiety p pear still more helpful, even if has no fundamental influence on the supply of blood to the heart

Monoamine-oxidase inhibitors were in roduced with initial account of great improvemen and relief of pain after heir use Unfortunately the major y of these laims do not stand p to mildly critical scrutiny since there is no comparison be een the drug and placebo La er reports ha e been conflicting and less enthusiastic especially hen control has also been used. Side effects with earlier drugs of his type were fairly common and sometimes severe so that search for other more powerful and less toxic compounds has resulted

Isocarboxazid (Marplan), one of the more recently introduced monoamine-oxidase inhibitors, has now been submitted to controlled trials. I the first report Isocarboxazid is compared with an identical placebo in 35 patients ith ngina of t least moderate severity The ondition was judged t be stable nd pa ients who were neurotic or ho had hist ry of infarction in the preceding 6 months were not accepted Eighteen patient derived ymptomatic benefit from isocarboxazid alone 5 from the placebo alone 7 from both drug

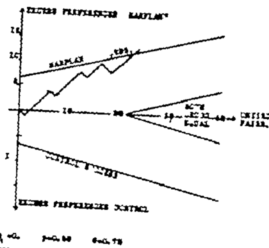


Fig. 1 Resul of sequen ial trial of soc boxazid. Default preferences for ontrol or drug only are plotted

nd plac bo nd he 23 othe ser ne ther treatment produced defi relief These results, al hough not impress re sat ally significant nd sugges hat isocarboxazid ha some nalgesic effect in ngina Analy is of he factors that influence good response show he drug t be most successful i pa ien who ha both severe angina nd cardiogr phic pict re of major ischemia without infar ion On of this group, 58 per cent thought hat the drug defi t l helped them. Those with ilder cases seemed be more fickle in their how whereas he major y of pa ient who had had previous infar ion found neither isocarboxazid nor he placebo of help The resul of 9 previously published ontrolled trials on other monoamine-oxidase nhibitors re summarized nd demonstrat only 2 significa successes so that ion is onsidered necessary i maki g la ms for isocarboxazid (Fig 1).

I second controlled rial[2] published soon afterward, isocarboxazid w gain sed on 50 patients. These resul show ha 14 patient f ored isocarboxazid nd 11 the placebo, whereas 14 patient dern ed benefit from both treatments, nd the other 11 were not influenced by either In this instance the difference betwee isocarboxazid and the placebo, lthough present is not statistically significant Side effect were minimal in the tw series with the daily dosage of 30 mg used, nd no changes resulted in either blood pressure or rdiogram.

Both these trials were conducted under double-blind conditions on within patient basis (each indi idual had both treatments nd acted as his own control), and the sequential method described by Armitage[3] determined the design. This type of statistical pproach is becoming increasingly popular with the clinical investigator who is able t follow the trend of his result and finish the trial when a conclusion is reached. Another advantage becomes appare t when omparison between report is needed nd similar t t tical background such urs in thi inst nc i then tremely helpf l Each of the trials had to satisfy 95 per ent pow r of detecting diff rence betwee the tw treatment t the 5 per cent signi nc lev l The criteria for ac pting suc es for isocarboxazid wer that 68 per ent of the patient had to find it d lue in the first trial nd 70 per ent in the second. Responses t the plac bo were expected in 40 per ent of the patient in the first trial, nd in 35 per t in the second The differenc found l the degrees of suc ess of isocarboxazid in gina in these tw compar ble report underlines the problem of even controlled trials, in which the rigid condition of the ideal experiment not be satisfied since there are no parallel objecti find ngs. Various methods of t ying to sess subjective response such as daily report cards nd hecks on trinitrin tablets, ha been used but g in these depend greatly on the patie t support. Ma y ndi iduals seem incapable of ooperati ng to the tent required for such result to be worth the t labor in ol ed. Object e criteria, such as exercise tolerance tests, do not alw y correspond t the anginal pain, nd indeed, are considered by number of workers to be both artificial and even dangerous.

I conclusion therefore the result quoted previously re not conflicting in showing that isocarboxazid ha some pparent analgesic effect in ngina although they differ as to the number of patient benefited, and in the second trial lg nific t difference was not found between the drug nd the inert substanc There s suggestion that it may be most successful in this respect in sufferers who ha severe pa nd cardiogr phic evidence of ischemia. The dramatic claims of preliminary trials are not re lly substa tiated, but, being rela ti ely free from side effects, isocarboxazid may help in certai cases. Caution is probably necessary ll the same for there is much to suggest that the action of monoamine-oxidase inhibitors is probably due t easing of nervou tension nd anxiety T eles t the threshold of pain without increasing the patient coronary blood flow is not without pot tial danger which must be t ken int accou t Some support for this iew is g en by Sandler experienc w th phenipr azine. H found that although the patient exercise tolerance tended t increase the severity of ischemic changes in the electrocardiogram was increased in some instances.

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Methyldopa in hypertension

The drugs that are t present ailable for the treatment of hypertension fall into two principal groups. The group of powerful drugs which reduce the blood pressure mainly when the patien is standing ar represented by the ganglion-blocking drugs and by guanethidine These drugs are life saving in the severest forms of hypertension but the regulation of dose is critical and they can easily cause severe orthostatic hypotension. At he other extreme are drugs such reserpine thiazides and hydralazine, which, either alone or in combination, ha a weak action on the blood pressure in many patients but are easier to use, and with cautious dosage are more easily tolerable. There is undoubt edly need for drugs ith intermedia properties to fill the gap between these tw groups. A new drug, alphamethyldopa (Aldomet), that has some novel pharmacologic properties may be partial answer to this problem. Methyldopa was y be- sized by Stein, Bronner and Pfister (1955)[1] during study of deriv tives of dih droxyphenylalanine which t was thought might interfere wi h the synthesis of noradrenaline. These todies were inconclusive, but subsequently Sourkes (1954)[2] showed that methyldopa inhibited the decarbox lation of dihydroxyphenylalanine (dopa) dihydroxyphenethylamine (dopamine), step i he main path- w y of synthesis of noradrenaline Dengler nd Reichel (1958)[3] showed that this compound was antihypertens in man, nd its mode of action as assumed t be the depletion of noradrenaline aused by reduction synthesis. Much careful pharmacologic work by Sjoerdsma Udenfriend[4-6] and their associa es has established that methyldopa is decarboxylase inhibitor in man, bu some doubt ha arisen whether this is he only or even the principal mode of ction. Tissue stores of noradrena line are depleted for much longer tha the inhibition of decarboxylation lasts, nd has been suggested that the main action ma be an al eration in he tissue binding of noradrenaline The main excretion of 3 methox -4-hydroxy mandelic acid is not constantly reduced b methyldopa, which also suggests that biosy thesis of noradrenaline ma not be affected

W ha recently completed he first yea of study of this compound i he Hypertension Cl at Hammersmith Hospital[10] When he drug as given as large single dose of 1 4 Gm orall or intravenously he h potensiv action began af er 4 to 5 hours nd lasted about 24 hours The onset of the hypotensiv effect was associa ed ith sedation. Fift nine pa ien er reated ith or f methyldopa for periods of p f yea About half had renal etiology nd in half the diagnosis was essential h pertension Twenty had etinal hemorrhages, exudates or papilledema and before tea men most patien had blood pressures ha ex ceeded 220/120 mm Hg The result w lassed satisfactory if he blood pressure was t or below 160/100 mm Hg when he pa ien as in either he ly or stand ng position on most follow p

visits. Treatment w judged to be satisfactory in 32 of the 59 patients, and there were more successes among those with less severe cases, particularly women than among those with more severe cases. The drug was given in di ided doses three or four times daily starting with 250 mg per dose. The erage dose in the successfully treated patients was 1.75 Gm daily the range being 0.5 to 4 Gm. Both he lying and the standing pressures fell, and there was usually a further fall when the patient was standing but this was not so great as was seen w th ganglion-blocking drugs or guanethidine. On exercise there was small fall in some patients but no large falls were seen as sometimes occur w th guanethidine Most patients had an even reduction in pressure throughout the day although postural hypotension occurred some while the dose was being adjusted

Treatment with methyldopa had t be abandoned in 17 patients, in 7 because the drug failed to control the blood pressure when the practical maximum dose of 4 Gm. daily had been reached. I 10 others some degree of control of pressure was achieved, bu his was not regarded as satisfactory either because of intolerance to side effects or because ischemia of brain or heart made the drastic reduc tion of blood pressure nwise The most common side effect was somnolence, but this then tended t wear off A few pa ients were left with mild sedation for longer periods nd several reported that they slept exceptionall soundly The most serious side effect was retention of fluid and pparent precipitation of heart failure in 7 patients. This action did not ppear be related to the degree of reduction of blood pressure nor to an elevation of the blood urea and its origin is mysterious. A similar complica ion sometimes occurs th guanethidine Other side effects included stuffy nose, dry mouth sore ongue depression, and nausea, but these symptoms occurred in only small proportion of the pa ients There wer no serious toxic reactions, except for one instance of thrombocytopenic pur pura hich was probably caused by sulfonamide given simultaneously for chronic pyelonephritis.

Studies of bsorption nd excretion of ^{14}C-labelled methyldopa were made in 11 patients. The excretion after intra enous doses as rapid, and almost the whole of the dose appeared in the urine thi 24 hours Excretion was much slower in pa ient th ele ted blood ureas, and w ha e encou ered one instanc of severe hypotension after the accumulation of the drug in patient hose renal function had w rsened Clearly it is important t increase the dose slowly hen he blood urea is high. P tients with normal renal f nction ho were gi en or l doses excreted almost exactl half the oral dose w thin the first 24 hours, and this probabl is indication of the amou t absorbed. Previous studies of absorption of the d,l racemat had show much smaller absorption, but this was probably because the d form is ery poorly absorbed.

The circulatory effect of the drug show some

evidence of sympathetic blockade particularly bradycardia and blockade of the overshoot after the Valsalva manoeuvre. Studies in progress with my colleagues, M. Harington and J. V. Hodge show that the response to noradrenaline is only slightly increased in amplitude but that the duration of elevation of pressure is greatly increased. There is also an increase in the pressor response to tyramine. These studies have also revealed that when the patient is in the resting supine position the cardiac output is not reduced by methyldopa although there is a fall in the blood pressure in this position. When the patient's feet are tilted down there is a fall in the cardiac output and further fall in the blood pressure.

Many problems of the clinical pharmacology of methyldopa remain to be elucidated, particularly the role of central action if there is one, but the position of the drug in therapeutics seems clearer. The drug does not appear to be particularly suitable for patients with malignant hypertension for some of these patients are resistant and others develop tolerance. The drug has many properties which make it particularly suitable for the patient with moderately severe hypertension who will not tolerate the side effects of ganglion blockers or guanethidine. Two questions remain to be answered: the incidence of tolerance and of toxic idiosyncrasies. Some tolerance occurs in many patients, although it can often be overcome by a moderate increase in dose or by the addition of a diuretic. However, tolerance may be a serious matter with a drug whose dose is usually high. Toxicity studies in animals indicate a very satisfactory margin of safety for the drug, but fever, hepatic dysfunction, and reversible agranulocytosis have been reported as isolated toxic reactions.[13] Further experience should answer these questions.

Methyldopa appears to be a useful addition to the spectrum of antihypertensive drugs. As the number of effective drugs increases, it becomes important to identify those patients who are likely to respond to any particular drug. Methyldopa may have its main use in the middle part of the range.

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Letter to the Editor

Proposal on possibility of improving cow's milk for the purpose of lowering the incidence of atherosclerosis

To the Editor

All are agreed that disease of the coronary arteries is a number one killer. Although the specific cause of hardening of the arteries is unknown, it seems reasonably clear that an excess of saturated fats is in some unknown manner correlated with an increase of atherosclerosis. It is likewise apparent that diets high in unsaturated fatty acids, or fat free, may be beneficial. But the nature of the benefit has not been clearly demonstrated. Since the American population consumes large quantities of cow milk, known to be rich in saturated fatty acids, and, hence, perhaps harmful, a thorough study by competent authorities may be fruitful and is briefly suggested below.

Four ideas may be considered, only one of which appear to be feasible. First, although goat milk is high in unsaturated fatty acids (and in this respect is like mother milk), the cost of wide-sweeping conversion of existing dairy facilities from cattle to goats would obviously be prohibitive. Second, it does not seem reasonable to attempt to re-educate the American public to the exclusive use of low-fat cow milk. Because low fat milk is relatively unsavory, most users of it appear to be dieters, health faddists, or those under doctor's orders. For example an unofficial survey conducted during the lunch hour at the Student Union at U.C.L.A showed that the majority of students were drinking whole cow milk. It would also appear that most of the coffee drinkers use cream. Third, there is apparently no simple, direct, and inexpensive method now available for unsaturating the fatty acids in cow milk.

This leaves us with the fourth and final suggestion. There may be a possibility of providing milk from cows which are genetically endowed with the ability to produce milk that is high in unsaturated fatty acid content. The success of such a program would depend upon two factors, namely the detection of individuals in which "good" milk is heritable and, second, a program of inbreeding and then the expansion of herds, from such selected cattle.

The detection of those cows which characteristically produce milk high in unsaturated fatty acids does not seem to be formidable. People trained to carry out routine tests for fat quantity and quality might analyze large numbers of samples of milk so that appropriate females might be selected. It is most important to note that such a program of selection is made reasonable by the fact that cow milk fat is highly heritable, that is, under strict genetic control. In other words, cows with a particular milk trait can be expected to transmit to their progeny the genes which determine that trait. Milk trait is apparently not influenced by such vagaries as environment and diet, factors which would be expected to vary in sampling milk from cows in different parts of the country. In order that selective breeding be accomplished, genetic variability for milk traits must be uncovered. Professor Clyde Stormont (University of California, Davis), an acknowledged authority on problems of cattle genetics, has stated (personal communication) that variations in the quality and quantity of fat can be reasonably expected not only between herds but between individuals in particular herds. In sum, it would appear that the *trait* can be detected, it is genetically controlled, and genetic variants may well be found. If so, a program of selection, inbreeding and expansion might lead to the desired results.

Another problem is that of the possible deterioration of natural vigor *in* the course of inbreeding. In some organisms, gross birth defects, atavism, stillbirths, and lowered *fertility* accompany the crossing of near relatives. Consultation with Professor Stormont on problems of cattle genetics lead to the conclusion that over-all vigor is not likely to be lost in inbreeding.

No large-scale experiment of the kind suggested here is known to be *underway* or under serious consideration according to Professor Richard Siegel (University of California, Los Angeles) and Professor Stormont. The idea seems simple, promising, and the most appropriate among those considered. After thorough study by a suitable governmental agency such as the United States Public Health Service, it might be explored more fully.

It is obvious that this is only one facet of the broad problem of atherosclerosis.

Myron Prinzmetal, M.D.

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Th l k l ses hre mem re ph b Uff re t t ngu ge wh h l l th sever l re d surg l res The b t se on "Some A pec d he R pair Pr M mmal w en l R ell nd Bill ham Th welle re se d the rre field of w und he l g ad rit l l sh l mphasi pla ed on the mon me he l d stud d wound he l g w h es hus m d mou tages d he l l fa wh h affe w und he l ng

The second sec on d he l k writt Germa by Haue nd Brendel de l w th the gener l field d hypothermia E tens exp ri mental tudies are described with emphasi on the de rmination d res l ime nd surv l time d mou org tem

The hird sec ion wri French l Mon so ngeon re d he f nct on of the adrenal cortex nd surgical pathology The arrou udies d l w th the prolonged response d the drenal rt l tem repe ed stresses. These arious studies are concerned w th h hl pe ialized subjec wh h w uld be of eres t est g tors w rk ng in hese pa ticular field This reviewer doubt ha the book w uld be of gener l terest t he majorit of readers d he Americ *Heart Jou nal*

The newer diagnostic proced res nd techniques such ardiac thet iz tion ngic ard g r phy phonoc d gr phy ballist card gr phy nd w f rth the by w thholding from the reader much d the im ort t knowled ac q ed th pa t decade n the field d card ology

The prese t med l l t r tur l t ext nus nd present med al knowledge t sophistic ted t j stif the add t on of book d th nature to the alread manageable stack d it on temporaries It ha little t ffer n r ma y of t predecessors published l past decades

The Book of Clinical Cardiology B Harold W Salmon M.D. M.R.C.P. Physicia t East Ham Memorial Hosp al nd Queen Mary Hospital for the East End London, 1962 Harvey & Bly he Ltd 184 pages. Price $3.50 (25 shillings).

As the ti le and preface mply thi book is written primarily for he gener l prac tioner nd house officer It is brief and q it simple outline of cardiology learly written for he most part and studded w th occasional quaint phrases and metaphors so that it is easy nd pleasant t read. However beyond these remarks, little can be said in it behalf Less complet and more elementary than ma y of the standard textbooks of medicine used by medical studen s, it is difficult to see how it could be of much help t the practicing physicia responsible for the care of sick people The patient would be n fortunat indeed if he were under the are of physicia who depended on this "handbook for his knowledge of cardiology I addi ion t it incompleteness, the discussion is frequently oversimplified t the point of distortion of truth and repeatedly contains grossly erroneous statements. The graphic techniques of cardiologic diagnosis are illustrated by a series of 10 chest x-ray films and half dozen or so electrocardiograms which are so patently typical as t be superfluous. In keeping with its simplified linical pproach, the book foregoes any discussion of

The Pulmonary Circulation. By Peter Harris M.D. Ph.D. (Lond.) M.R.C.P. Senior Lecturer in Med ne Uni rsit of Birmingham Queen Elizabeth Hospital, Birmingham d Donald H h M.D. (Sheff.) Ph.D. (Birm.) M.R.C.S. L.R.C.P. Sen r Lecturer in l thology Uni rsity d Birmingham, Birmingham England Baltimore 1962 William & Wilkin Compa y 351 pa es Pri $11.50

Th is well-w itten book y t read l pro f ssfully st ted nd the ill st tion are d good qualit The authors are keenl w re d the problems in d d the determina ion of pul monary s lar resistance from pressure nd flow me su emen the h ma subjec nd make this problem q lear t the reade There is thorough d scussion of the tech al problem nd the sources of error in he me surement of pulmonary blood flow There is onc se discussion d the effect of drus nd respir tory g ses on the pulmonary irculation, followed by several hapters which deal with the auses and mecha ism of pulmonary hypertension There is horough description of the bronchial ir la tion nd of the influenc of dise se d the l ngs pon the pulmonary ir lation.

The only short oming that I find in the book are those of omission. Missing are sev al topic which one might ha expected to find in monog ph on the pulmonary circulation. T some extent the omission of these topics resul from the uthors self-imposed limitation of their text t studies of the human pulmonary circu lation.

A discussion of the effects of pressor age pon shu t nd murmurs in patient w th entricular septal defect nd patent ductus arteriosu would ha been of interest. The description of hemodynamic effect of pinephrine and nor epinephrine suffer because of the omission of animal experiment which demonst t lear asoconstricti action.

I found the description of primary pulmonary hypertension t be ther brief nd thought that a more adequat discussion of the differential diagnosi of pulmonary hypertension could ha been included. I found no discussion to whether the pulmonary circulation ha filtar f nction. In the chapter on the discussion of the mes of

pulmonary hypertension, I should have liked more thorough description of the hemodynamics of left ventricular decompensation, especially with regard to the effects of digitalis and with regard to the comparison of left heart failure with mitral stenosis. In the chapter on pulmonary hemodynamics of mitral valve disease some description of cor triatriatum might well have been in order. I believe that some discussion of the patient with higher cardiac output and higher pulmonary vascular pressures in mitral stenosis in contrast to those with similar valve disease with lower outputs and pressures should be included. I would doubt that patients with mitral stenosis invariably have such relation between pulmonary wedge and pulmonary arterial pressure as depicted in the authors' graph. In the discussion of the anatomy of the pulmonary circulation, I looked for but was unable to find a description of pulmonary arteriovenous anastomoses. The authors might have discussed the postulate that arterial constriction can simulate increased thickness of the media and elastic lamina. I believe that description of pulmonary edema might be included in a book on this subject. In describing the cyanosis of pulmonary hypertension caused by recurrent pulmonary embolism, the authors might have considered opening of the foramen ovale or of pulmonary arteriovenous anastomoses as alternative explanations.

Despite the above-mentioned omissions, I believe that the material contained within the book compensates for these shortcomings. The presentation seems to be thorough and well grounded in the areas that it covers. The book can be recommended without reservation to those interested in the anatomy, physiology, and pharmacology of the pulmonary circulation.

CARDIOVASCULAR FUNCTIONS. Edited by Aldo Luisada, New York, 1962, Blakiston Division, McGraw-Hill Book Company, Inc. 332 pages. Price $12.

This is a strange book. It is especially difficult to justify since most of it has already been published previously.

The Preface states that it is directed to physiologists, research workers, teachers, etc., but in most cases the coverage is so superficial as to be practically useless to anyone who is well versed in the subject. It does provide a sort of general coverage of many topics. As one reads through it, he is reminded of Eric Neil's comment, originally attributed to Sir Thomas Lewis, I think, who said that there is much about this which is both good and new, but that which is good is not new, and that which is new is not good.

I think that some of the discussions are unfortunately very poorly chosen. Many of the authors are old and semiretired, or at least not active, and their contributions reflect their recent absence from the field. Much of what they have to say is of purely historical interest. It is hard to justify the two separate chapters, one by Burton and one by Rodbard, both of which essentially discuss identical topics. In addition to being largely erroneous, Holman's chapter contributes nothing.

On the other side of the ledger, Eric Neil's chapter provides more information on reflexes than do most textbooks, and it is healthy to see a chapter on this general subject included. The chapter on physiology of small vessels I regarded as quite good. This subject is usually lost, or even ignored, in books of this type.

It is inconceivable how a book of this nature could have been put out without having at least one chapter by Rushmer.

ARTERIAL HYPERTENSION AND ISCHEMIC HEART DISEASE. PREVENTIVE ASPECTS. WHO Technical Report Series No. 231. Geneva, 1962, World Health Organization, 28 pages. Price $0.30.

This small booklet of 28 pages summarizes the contemporary views of a Committee of International Experts which met in Geneva during October 1961. The objectives of the Committee was to summarize the present state of knowledge and to indicate fields for research in the future in the prevalence and treatment of these conditions.

The text is extremely concise and compressed yet reads easily. The section on hypertension deals with the techniques of measurement of blood pressure, the definition and grading of the disease, and the known causes. Prevention of the disease is hampered by our lack of knowledge, and much work still needs to be done on assessing the efficacy of therapy. Thus, there are ample fields for research.

The section on ischemic heart disease is concerned with the classification of the clinical syndromes and the diagnostic criteria. Prevention and treatment of this condition is clearly still entirely controversial. There was little disagreement among the Committee members about the usefulness of anticoagulant therapy, but this view cannot remain unchallenged, and much work is still required to assess the efficacy of this and any other form of therapy.

The booklet is recommended to any physician interested in the field of hypertension and ischemic heart disease, and should thus have a very wide audience.

Announcements

\ I D \ C st rs Ei ocardi r rhy (Ad nced Electro rd iog will be offered by the Un ersity of N br ska Colleg of Med ne Febru ary 4 nd 1963 Omaha N b Guest facult for he u se ll be Dr J A Abildskov of the Upst t Med al Center Sy a se N Y nd Dr D A B d of he U ersity of Tennessee

Ad nced regis r on ma be made b writ ng Medical E en ion U ersit of N br ka Colle of Medi ne 42 nd Dewey Omaha 5 N b.

C d ists who do some of their ow diagnostic r work re i ed t ttend the AN AL MEET I G OF THE AMERIC SOCIETY OF CLINICAL RADI or s t be held J 28 and 29 1963 t the Soreno Hotel i St Petersburg Fla

NEW CRA PROGRAM C RDI ASCUL DISEASE The dairy ndustry announces the establishment of pecial grant research program for the in estigat on of the potential role of dairy products in the development of ardiov scular disease. Special tention will be directed t ard the metabolic beha or of different dairy product r ter actions between dairy product omponent with reg rd lipid metabolism, the development of therosclerosis or thrombus forma ion in suitable experimental nimals or man S udies concerning the nutritional alue of milk fa or the factors modif ing the pr portions of the major or minor component of dairy foods influencing dairy fat utilization also ma be considered. I estigations which imultaneousl provide f ndamental information about dietary fac ors in ardiovascular disease nd also provide guidance for the development of nutritionally superior dairy products are particularly encouraged

This program is t be administered by Special Dairy Industry Board representing all segments of the dairy industry scientific guidance will be provided by committee of outstanding scientists from academic government and dairy industry laboratories.

Interested investigators in medical or university labor tories should pply to Dr Merrill S. Read Secretary Scientific Ad isory Committee, Special Dairy Ind try Boa d, 111 North Canal Street Chic go 6, Ill.

THE I STITUTE FOR ADVA CEMENT OF MEDICAL COMMUNICATI N reviewing ndidates for its program t trai workers for research nd dev lopment i the field of biomedical communication. Applica t for traineeships hould ha a substa tial educa tional background in the biological, physical, or social sciences, or extensi experience w th information services for scienti t or phy icians. A Ph D or M D degree nd research experienc are de irable but not essential. Training stipends ar flexible

Inquiries should be addressed t Dr Richard H. Orr Director Instit te for Ad ncement of Medical Communication, 9650 Wiscons Ave., Bethesda, 14 Md

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Erratum

In the article "The Polarcardiograph An Analogue Computer That Provides Spherical Polar Coordinates of the Heart Vector" by A D Moore Ph.D., P Harding B.A.Sc., and G E. Dower M.B B S. which appeared in the September 1962 issue of the Journal the statement on page 38 that the computer of Abildskov and associates provided information about the QRS complex only is incorrect ac cording to word received by Dr Dower f om Dr Abildskov

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Editorial

Glycogen storage disease of myocardium

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Glycogen storage disease of the myocardium is a rare familial error of metabolism in which glycogen accumulates in the myocardium and other tissues. In 1932 Pompe,[1] in Holland and Putschar and Bischoff in Germany[2,3] independently described infants with enormous hypertrophy of the heart due to excessive quantities of glycogen distributed diffusely throughout the myocardium Since then a total of 54 well-documented cases of cardiac glycogenosis has been reported. The salient clinical pathologic and biochemical features have recently been reviewed and may prove helpful in differentiating this disease from other primary endomyocardial conditions of infancy such as endocardial fibroelastosis, myocarditis, tumors of the heart, anomalies of the coronary circulation and idiopathic hypertrophy

The cardiac type of glycogen storage disease is one of a group of diseases with glycogenosis of one or more organs or tissues. Stetten and Stetten have divided this group into six types based on the enzymatic deficiency demonstrable and or the clinical pattern exhibited by the disease. In all but Types III and IV the glycogen is structurally normal Type I the hepatorenal type described by von Gierke in 1929 involves the deposition of excessive quantities of glycogen in the liver and frequently in the kidneys. It is due to a deficiency of the enzyme glucose-6-phosphatase Type II the cardiac type with generalized glycogenosis consists of the accumulation of glycogen in excessive amounts in all tissues, but especially in the myocardium

In Type III limit dextrinosis, described by Cori an abnormal glycogen with short outer branches accumulates in the liver and skeletal as well as cardiac muscle This is due to an absolute lack in muscle and liver of the specific debranching enzyme, amylo-1 6-glucosidase. Type IV amylopectinosis, was described in a single case by Andersen. Here an abnormal glycogen with few branch points was present in a cirrhotic liver and in the reticuloendothelial system Insufficient material was available for enzyme studies, but the biochemical findings suggested the disorder to be a deficiency of the branching enzyme amylo-1 4→1 6-transglucosidase.

Type V the muscle type, was described by di Sant Agnese in a child with muscular weakness but no evidence of cardiac involvement. A muscle biopsy revealed structurally normal glycogen in large quantities. Permission for autopsy was refused Since no determination of phos-

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phorylase was made, this case may be similar to the defect classified below as Type VIb. Type VI, the phosphorylase type, can be subdivided into a hepatic (a) and a muscle (b) type. In the hepatic form described by Hers, glycogen is deposited in the liver, and the level of hepatic phosphorylase is reduced. In the muscle type described by Schmid and co-workers and Mommaerts and co-workers, myopathy is associated with the deposition of glycogen in muscle. Muscle phosphorylase is almost completely absent.

In cardiac glycogenosis the specific metabolic error has not yet been elucidated. Not only is the glycogen normal in structure, but the known tests of carbohydrate and fat metabolism are normal also. It is important that postmortem examination of patients suspected of having this disease be performed as quickly as possible, with tissue frozen immediately for analysis for the percentage of glycogen as well as for the structure of the glycogen and the determination of specific enzyme defects. Myocardial glycogen content so analyzed in the 6 most recently reported cases has been greater than 5 per cent of the wet weight of the tissue (normal 0.77 per cent).

Pathologically, cardiac glycogenosis results in enormous hypertrophy of the ventricles, especially the left ventricle. Heart weight has varied from 2 to 6.5 times (average 4 times) the normal weight expected for age. Ventricular thickness has ranged from 2 to 25 mm. (average 7 mm.) for the right ventricle and from 4 to 32 mm. (average 16 mm.) for the left ventricle. Microscopically, the massive uniform deposition of glycogen causes swelling and vacuolization of the myofibers, giving a "lacework" appearance that is characteristic.

Deposition of glycogen occurs in all other tissues, including skeletal muscle. This offers a means of diagnosis during life by skeletal muscle biopsy with examination for the typical pattern of muscle degeneration and the presence of an abnormal amount of glycogen. To do this, a portion of the tissue should be fixed promptly in absolute alcohol for staining with Best's carmine stain or periodic acid Schiff stain with diastase digestion, and the remainder frozen for more detailed biochemical analysis if indicated.

In 1950 di Sant'Agnese, Andersen, and Mason[4] reviewed the literature on glycogen storage disease of the myocardium and set forth the following criteria for diagnosis: (1) marked enlargement of the heart, (2) typical "lacework" appearance of histologic sections of the myocardium, (3) chemical or histochemical demonstration of glycogen as the material causing infiltration of the myocardial fibers, and (4) death within the first year of life. In 1959, di Sant'Agnese[7] modified these criteria to require the demonstration of a normal structure of the deposited glycogen, thus excluding cases of limit dextrinosis (Type III) in which there is no cardiac enlargement or dysfunction. We eliminated the fourth criterion since patients have lived beyond the first year and for as long as 14, 17, and 34 months.

Review of 54 authentic cases[1] has shown that the condition occurs equally in both sexes as a familial disorder. No parent was reported to have the disease, although there were 10 instances of proved involvement of two or three siblings, and 13 instances in which it was likely that siblings or other relatives who died in infancy had the condition.

Symptoms were usually noted by 2 months of age, and death occurred at an average age of $5\frac{1}{2}$ months (range stillborn to 34 months). Cardiomegaly and dyspnea were the two most prominent features and were often associated with hepatomegaly, cyanosis, and muscular weakness. A slow gain in weight and difficulty in feeding were frequent. Half had pulmonary complications. Hypotonia and muscular weakness were so severe in 15 cases that the diagnosis of a primary neurological or muscular disorder was considered. Because of macroglossia in addition to hypotonia, the diagnosis of Mongolism or cretinism was entertained in 5 cases.

A systolic murmur was described in 26 infants, but unfortunately few details were given concerning the murmur, heart sounds, or presence of gallop rhythm. Cardiac enlargement was so marked that on roentgenograms, the heart frequently filled most of the left side of the chest.

Analysis of electrocardiograms available in 21 proved cases showed the following characteristic features of diagnostic im-

portance (1) a short PR interval (2) wide amplitude of all deflections, QRS and T and (3) left ventricular hypertrophy. Although the earliest published records showed T waves deeply inverted and ST segments depressed these findings are not always present. Several recent cases have had T waves of normal direction in limb and precordial leads.

A previously unrecognized feature of cardiac glycogenosis that of obstruction of the left ventricular outflow tract was demonstrated by hemodynamic evaluation in an infant with a murmur suggestive of aortic stenosis. Catheterization of the right side of the heart showed only slight pulmonary hypertension of 35/13 mm. Hg but simultaneous pressures in the left ventricle and femoral artery showed a systolic pressure gradient of 158 mm. Hg. Analysis of the tracings indicated that the stenosis was due to subaortic muscular hypertrophy since little or no resistance to outflow was noted in early systole but with progressive contraction a marked obstruction developed which virtually shut off outflow from the left ventricle and led to a rapid fall-off of arterial pressure and a low diastolic pressure. From the pathologic findings of enormous left ventricular hypertrophy so consistently present in cardiac glycogenosis, the development of obstruction to outflow from the left ventricle might be anticipated in others. This obstruction could in turn cause further hypertrophy of the muscle and increasingly greater obstruction of the outflow tract. This case represents one of the few instances of obstruction of the left ventricular outflow tract in which the etiology of the myocardial hypertrophy has been proved.

In summary cardiac glycogenosis is one of a group of errors of carbohydrate metabolism that is beginning to be clarified and it is one of a group of primary endomyocardial disorders of infancy that is beginning to be understood hemodynamically and that can be diagnosed during life. Palliation may come through intensive medical management of the heart failure or through surgery to relieve the obstruction of the outflow tract. Cure must await further delineation and then appropriate modification of the metabolic abnormality.

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Clinical communications

Observations concerning progressive pulmonary vascular obstruction in children with ventricular septal defects

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The complete spectrum of the natural history of ventricular septal defect is not fully documented but it includes patients who show no evidence of progressive pulmonary vascular obstruction as well as those who do. Among those who have such evidence the rapidity with which obstructive changes progress varies.

The presence of pulmonary vascular obstruction is important because successful surgical correction of ventricular septal defects with present techniques depends on the ratio of pulmonary flow to systemic flow being greater than one. When obstructive changes in the pulmonary vascular bed have progressed until pulmonary flow no longer exceeds systemic flow surgical correction by present techniques is not recommended because of the high risk.

Several authors[1-3] have stated that progressive pulmonary vascular obstructive disease practically never occurs during childhood. This idea has been given as one reason that surgical repair of ventricular septal defects need not be considered during infancy or early childhood and that conservative treatment need occasion no fear. On the other hand Lucas and coworkers[4] recently published results of serial physiologic studies of children with isolated ventricular septal defect including 4 who showed apparent progressive pulmonary vascular obstructive disease.

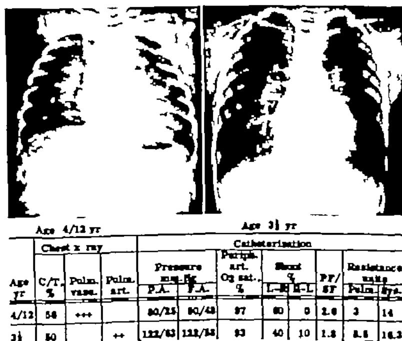
Most information on the natural history of ventricular septal defect has been derived from data obtained from infants and children by repeated cardiac catheterizations. These data are of value and currently are being accumulated in serial studies on individual patients in many medical centers. However our experience in calculating pulmonary blood flow from data obtained by cardiac catheterization and subsequent observation of the hemodynamic response of 436 children with ventricular septal defects to surgical treatment has demonstrated the validity of correlating electrocardiographic roentgenologic, and other clinical features with calculated pulmonary blood flow and pulmonary vascular resistance.[5,6] Accurate assessment of these factors, in fact can be made by careful evaluation of serial roentgenographic or electrocardiographic studies of individual patients. Thus the natural history of ventricular septal defect in children can be documented by data obtained by these methods as well as by cardiac catheterization.

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Patients with large ventricular septal defects, without pulmonary vascular obstruction have predominantly left-to-right shunts. This is reflected in roentgenograms of the chest by cardiac enlargement and increased prominence of pulmonary vascular markings in the middle and peripheral regions of the lung. With the development of severe pulmonary vascular obstructive disease pulmonary vascular resistance approaches systemic vascular resistance and the left-to-right shunt diminishes—in fact the shunt may be reversed. Roentgenograms of the chest (in the presence of severe pulmonary vascular obstructive disease) demonstrate diminution in the size of the heart and in the prominence of peripheral pulmonary vascular markings, *an increase in prominence of the pulmonary* artery segment and no change in the prominence of hilar shadows. These roentgenographic observations have been studied in relation to cardiac catheterization data and reveal reasonable correlation of the size of the heart, size of the pulmonary artery segment, and prominence of the pulmonary vascular markings with the calculated ratio of pulmonary flow to systemic flow.[4] (The cardiothoracic ratio in infants under 6 months of age may normally be somewhat greater than 50 per cent; this must be considered when one evaluates progressive changes in cardiac size.)

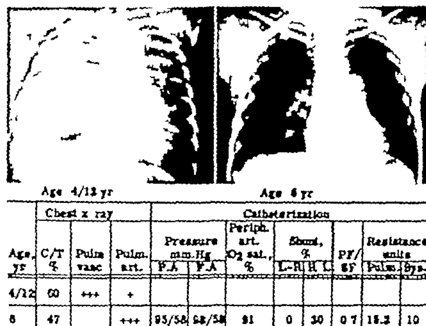
Patients and methods

This report concerns 7 children with ventricular septal defects who were studied from November 1960 through April 1961. Roentgenologically, each demonstrated evidence of progressive pulmonary vascular obstruction between infancy and the age of 10½ years by significant changes in the size of the heart and main pulmonary artery and in the prominence of pulmonary vascular markings. All, *at one time, had* roentgenologic evidence of increased pulmonary blood flow. Cardiac catheterization of the children at 3½, 6, 6½, 8½, 10, 10, and 10½ years of age, respectively, revealed severe pulmonary hypertension with calculated pulmonary and systemic blood flows and resistances which indicated severe obstructive pulmonary vascular changes.



Age yr	Chest x-ray			Catheterization								
	C/T, %	Pulm. vasc.	Pulm. art.	Pressure mm. Hg P.A.	Pressure mm. Hg F.A.	Periph. art. O_2 sat., %	Shunt % L-R	Shunt % R-L	PF/SF	Resistance units Pulm.	Resistance units Sys.
4/12	58	+++		80/25	80/40	97	60	0	2.0	3	14
3½	50		++	122/83	122/58	93	40	10	1.3	8.6	16.3

Fig. 1. Roentgenograms demonstrate diminution of cardiac size and pulmonary vascular markings between the ages of 4 months and 3½ years. Cardiac catheterization data demonstrate decrease in calculated ratio of pulmonary to systemic flow with an increase in calculated pulmonary resistance and development of a right-to-left shunt.



Age, yr	Chest x ray: C/T %	Chest x ray: Pulm vasc	Chest x ray: Pulm. art.	Catheterization: Pressure mm.Hg P.A	Pressure mm.Hg F.A	Periph. art. O_2 sat., %	Shunt, %: L-R	Shunt, %: R-L	PF/SF	Resistance units: Pulm.	Resistance units: Sys.
4/12	60	+++	+								
6	47		+++	95/58	98/58	91	0	30	0.7	15.2	10

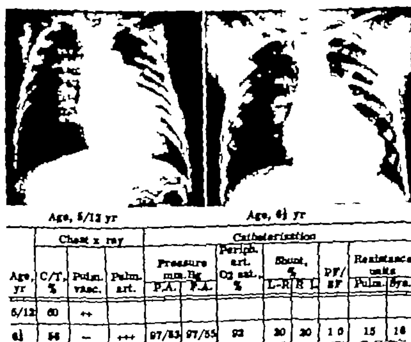
Fig. 2. Roentgenograms demonstrate a decrease in cardiac size with decrease in cardiothoracic ratio from 0.60 to 0.47 and decreased pulmonary vascular markings with increase in size of main pulmonary artery between 4 months and 6 years of age. Cardiac catheterization at 6 years shows blood pressure and flow measurement indicating severe pulmonary vascular obstruction.

Report of cases

Case 1 (*Fig. 2*). This patient born of a normal pregnancy was found to have a murmur when 2 weeks of age. Cardiac enlargement was noted on roentgenogram of the heart at about the same time. Digitalis therapy was instituted for cardiac failure which occurred when the patient was 6 weeks old. The patient grew slowly and had many acute respiratory infections. A roentgenogram of the chest showed cardiomegaly, minimal increase in the size of the main pulmonary artery, and a marked increase in the prominence of pulmonary vascular markings when the patient was 4 months of age. Cardiac catheterization revealed that the systolic pressure in the pulmonary artery was nearly equal to that in the femoral artery. There was a large left-to-right shunt at the ventricular level, with a calculated ratio of pulmonary flow to systemic flow of 2.6; the calculated pulmonary resistance was significantly less than the systemic. At the age of 3 years, the child was physically active without symptoms and he suffered from fewer respiratory infections. Six months later a roentgenogram of the chest showed that the heart had diminished in size and that the pulmonary artery segment had increased somewhat in size; the pulmonary vascular markings at this time were only minimally increased. Catheterization of the right side of the heart revealed equal pressures, systolic and diastolic, in the pulmonary and femoral arteries. Shunting through the defect was bidirectional, and the calculated ratio of pulmonary flow to systemic flow had decreased to 1.8; the calculated pulmonary resistance had increased in relation to systemic resistance.

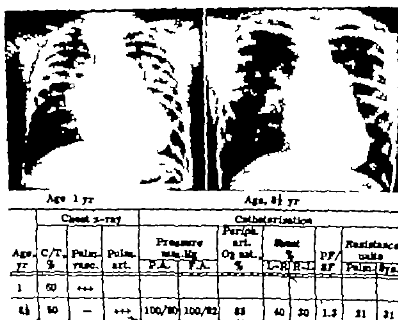
Roentgenograms of the chest and catheterization of the right side of the heart demonstrated in this patient that there had been progressive pulmonary vascular obstruction with significant diminution of pulmonary flow in 3 years.

Cases 2 through 7 (*Figs. 2-7*). These cases are similar in that each patient had at least two roentgenograms of the chest during childhood and catheterization of the right side of the heart at the time of the second, or subsequent, roentgenogram. Physical examination at the time of the second roentgenogram was also similar in all patients. The heart was quiet and the second heart sound in the pulmonary area was narrowly split with marked increase in the intensity of the pulmonary component. There was a short Grade 1 to 2 systolic murmur along the lower left sternal border and no diastolic murmurs were heard at the apex. At the ages of 4 months, 3 months, 1 year, 2 years, 6 months, and 4 years, respectively, roentgenograms showed an increase in heart size with moderate to marked increase in pulmonary vascular markings and only minimal increase in the size of the pulmonary artery segment. Roentgenograms of the chest at 6, 6½, 8½, 10, 10, and 10½ years of age, respectively, showed diminution in cardiac size and pulmonary vascular markings and an increase in size of the main pulmonary artery segment. Catheterization of the right side of the heart in each of the patients at the time of the second or subsequent roentgenographic examination revealed equal or



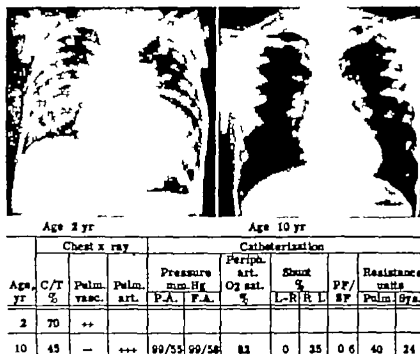
Age, yr	Chest x-ray: C/T, %	Chest x-ray: Pulm. vasc.	Chest x-ray: Pulm. art.	Catheterization: Pressure mm. Hg P.A.	Catheterization: Pressure mm. Hg F.A.	Catheterization: Periph. art. O2 sat., %	Catheterization: Shunt, % L-R	Catheterization: Shunt, % R-L	Catheterization: PF/SF	Catheterization: Resistance units Pulm.	Catheterization: Resistance units Sys.
5/12	60	++									
6½	56	–	+++	97/53	97/55	92	30	30	1.0	15	16

Fig. 3. Roentgenograms demonstrate change in size of the heart and main pulmonary artery and pulmonary vascular markings, indicating diminution of pulmonary blood flow between 5 months and 6½ years of age. Cardiac catheterization reveals equal bidirectional shunts and a calculated ratio of pulmonary to systemic flow of 1.0.



Age, yr	Chest x-ray: C/T, %	Chest x-ray: Pulm. vasc.	Chest x-ray: Pulm. art.	Catheterization: Pressure mm. Hg P.A.	Catheterization: Pressure mm. Hg F.A.	Catheterization: Periph. art. O2 sat., %	Catheterization: Shunt, % L-R	Catheterization: Shunt, % R-L	Catheterization: PF/SF	Catheterization: Resistance units Pulm.	Catheterization: Resistance units Sys.
1	60	+++									
8½	50	–	+++	100/80	100/82	85	40	30	1.3	21	21

Fig. 4. Roentgenogram taken when patient was 1 year old shows large heart with increased pulmonary vascular markings, indicating significant increase in pulmonary blood flow. The heart at age 8½ years, has decreased in size, and prominence of the pulmonary artery segment has increased. Cardiac catheterization data, at same age, show equal systemic and pulmonary arterial pressures, minimal increase in calculated pulmonary blood flow and marked elevation of calculated pulmonary resistance.



Age, yr	Chest x ray: C/T %	Chest x ray: Pulm. vasc.	Chest x ray: Pulm. art.	Catheterization: Pressure mm Hg P.A.	Pressure mm Hg F.A.	Periph. art. O_2 sat. %	Shunt % L-R	Shunt % R-L	PF/SF	Resistance units Pulm.	Resistance units Sys.
2	70	++									
10	45	—	+++	99/55	99/58	82	0	35	0.6	40	24

Fig. 5. Large heart and increased pulmonary vascular markings at 2 years of age indicate definite increase in pulmonary blood flow. Small heart and clear lung fields and cardiac catheterization data at 10 years of age reflect severe pulmonary vascular obstruction.

nearly equal pressures in pulmonary and systemic circuits and minimal to moderate desaturation of peripheral arterial oxygen. A right-to-left shunt through the ventricular septal defect was demonstrated in all of the patients, and the calculated ratio of pulmonary to systemic flow was 1 or less in each case, except Case 4 (Fig. 4), in which the ratio was 1.3. Also the calculated pulmonary resistance was equal to or greater than systemic resistance in all but Case 4. In Case 4 the pulmonary resistance was considerably elevated and approached the systemic resistance.

Comment

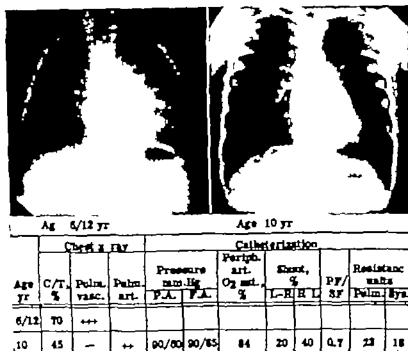
These 7 children with ventricular septal defects had progressive pulmonary vascular obstruction at some time before the age of 10½ years, as demonstrated by changes in the size of the heart and main pulmonary artery segment and in the prominence of the pulmonary vascular shadows apparent on roentgenograms. At an earlier time each had had roentgenographic evidence of increased pulmonary blood flow. Cardiac catheterization of each child revealed severe pulmonary hypertension with hemodynamic evidence of pulmonary vascular obstruction. Such obstruction represented a change during childhood from a physiologic situation favorable to operation to one that was less favorable in Cases 1 and 4 and unfavorable to operation by present techniques in the other cases.

From these examples, it is apparent that some patients with ventricular septal defects have rapidly progressive pulmonary vascular obstruction in early childhood. In an effort to prevent the development of these changes, surgeons should attempt early surgical repair of the defects of such patients. The relative size of the group requiring early operation is not known, but its existence indicates that concern for progression of pulmonary vascular disease should be an important factor in determining treatment.

We want to emphasize that these patients reveal only a portion of the spectrum of the natural history of ventricular septal defect; therefore, it should not be inferred that we recommend early operative repair in all cases. Each child must be evaluated individually; his treatment should relate to his position in the spectrum.

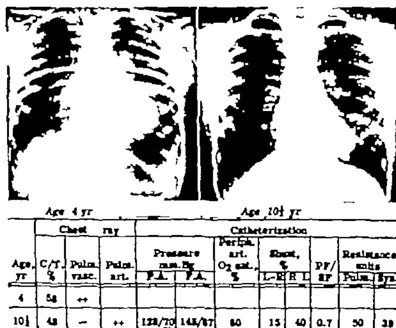
Summary and conclusion

Some patients with ventricular septal defect develop progressive pulmonary vas-



Age yr	Chest x ray: C/T, %	Chest x ray: Pulm. vasc.	Chest x ray: Pulm. art.	Catheterization: Pressure mm. Hg P.A.	Catheterization: Pressure mm. Hg F.A.	Periph. art. O_2 sat., %	Shunt, % L-R	Shunt, % R-L	PF/SF	Resistance units Pulm.	Resistance units Sys.
6/12	70	+++									
10	45	–	++	90/60	90/65	84	20	40	0.7	22	18

Fig. 6. A decrease in the cardiothoracic ratio from 0.70 to 0.45 and diminution of pulmonary vascular markings indicate decrease in pulmonary blood flow from 6 months to 10 years of age. Cardiac catheterization at 10 years of age shows evidence of predominant right-to-left shunt through the defect with pulmonary flow less than systemic.



Age, yr	Chest x ray: C/T, %	Chest x ray: Pulm. vasc.	Chest x ray: Pulm. art.	Catheterization: Pressure mm. Hg P.A.	Catheterization: Pressure mm. Hg F.A.	Periph. art. O_2 sat., %	Shunt, % L-R	Shunt, % R-L	PF/SF	Resistance units Pulm.	Resistance units Sys.
4	58	++									
10½	48	–	++	128/70	145/87	80	15	40	0.7	50	38

Fig. 7. Roentgenograms of the chest demonstrate decrease in heart size and pulmonary vascular markings between 4 and 10½ years of age. Cardiac catheterization indicated severe pulmonary vascular obstruction, with calculated pulmonary resistance in excess of systemic.

cular obstruction during early childhood Whenever such obstruction becomes so severe that pulmonary flow no longer exceeds systemic flow surgical correction by present techniques is not recommended because of the high risk In studying patients to detect evidence of progressive obstruction one can accurately assess the pulmonary blood flow and pulmonary vascular resistance by reviewing roentgenograms of the chest or electrocardiograms.

Seven children with ventricular septal defects who developed severe pulmonary vascular obstruction are the subjects of the present study All had early roentgenographic evidence of increased pulmonary blood flow consisting of cardiac enlargement and increased pulmonary vascular markings in the middle and peripheral lung fields. In each case subsequent roentgenographic findings indicated pulmonary vascular obstruction as did the results of cardiac catheterization studies. Calculations from data obtained during cardiac catheterization revealed a low ratio of pulmonary flow to systemic flow and elevation of pulmonary vascular resistance in relation to systemic vascular resistance roentgenograms at a corresponding time revealed decreased size of the heart and peripheral pulmonary vascular markings, with an increase in the size of the main pulmonary artery segment.

Since some patients with ventricular septal defect develop progressive pulmonary vascular obstruction in childhood this possibility must be considered in the management of infants and children with this congenital cardiac defect. Early operative treatment should be recommended for those patients who have evidence of progressive pulmonary vascular obstruction Each child deserves individual evaluation and management in accordance with his position in the spectrum of the natural history of ventricular septal defect.

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The electrocardiographic and vectorcardiographic findings in idiopathic hypertrophic subaortic stenosis

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The recent delineation of idiopathic hypertrophic subaortic stenosis as an entity has been followed by reports of cases from several laboratories. The number of these reports and the experience of the authors lead to the conclusion that this is a commonly overlooked syndrome.

The mechanism of production of the lesion is still obscure. The most commonly suggested hypothesis is that the lesion results from asymmetrical hypertrophy of the ventricle producing obstruction of the outflow tract.[3] An abnormal sequence of contraction of the major structural units of the ventricular muscle has also been suggested. The frequent observation of major electrocardiographic abnormalities in the syndrome has led the authors to consider the possibility that conduction abnormalities leading to an abnormal sequence of contraction may play a role in its production.

These speculations have led us to survey the electrocardiographic and vectorcardiographic findings in 8 proved cases and in 2 suspected cases of subaortic stenosis; the latter two patients were members of the family of one of the patients who had proved subaortic stenosis. These observations are the basis of this report.

Material and methods

The clinical data on the 10 cases are summarized in Table I. Cases 1 through 8 are considered to be proved cases in that (1) a definite left ventricular to aortic gradient was established by catheterization of the left side of the heart, (2) the gradient was localized to the outflow tract below the aortic valve, (3) cineangiograms or angiocardiograms demonstrated the absence of any fixed obstruction of the outflow tract of the left ventricle, and (4) a fall in arterial pulse pressure was seen in the beat that followed premature ventricular contractions as described by Brockenbrough and associates.

Case 8 was of interest in that the obstructive lesion was demonstrated only after the intravenous administration of isoproterenol. This patient is to be reported on in more detail in a separate communication.

Two patients (Cases 9 and 10) were members of the family of another patient (Case 1) and although these 2 cases were

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Received for publication Ma[illegible] 24, [illegible]962.

Table I Clinical data in Cases 1 10

Case	Age (yr.)	Sex	Race	Family history	Syncope	Congestive failure	Ejection murmur	Apical heat pa
Diagnosis established								
1	4	M	W	+	0	+	+	+
2.	1	M	W	0	+	0	+	0
3	35	M	W	+	+	+	+	+
4	30	F	W	+	+	+	+	+
5	18	F	W	+	+	0	+	0
6	42	F	N	+	0	+	+	+
7	44	M	W	0	0	+	+	+
8.	36	M	N	+	+	0	+	0
Diagnosis not proved								
9	49	M	W	+ (Sibling of 1)	+	+	+	+
10	12	F	W	+ (Daughter of 1)	0	0	+	0

Table II Electrocardiographic data in Cases 1 10

Case	PVC	P-wave abnormality	ST T abnormality	QRS abnormality	Remarks
1	0	+	+	0	Large P w es S-T ↓ in I II T flat in V
2.	0	+	+	+	QS in II III aV tall, broad R in V Q of 0 04 sec. in V V
3	0	+	+	+	40-mm. S w in V no R wa e in V 1-mm. R wa e in V QRS-T angle 180 degrees
4	0	0	+	±	25-mm. S wa in V R wa es small in V
5	0	+	+	+	ST T ↓ in II III Q wa e of 0.04 sec. duration in III V no R in V T diphasic in V, 50-mm. S wa e in V
6.	0	+	+	+	First-degree A V block S-T ↓ in I II V, V 50-mm. S wa in V T inverted in V, no R wave progression from V to V
7	0	+	+	+	Very large P w ves QS deflection in V very small R in V, QRS-T angle 180 degrees
8.	0	+	+	+	0.03-sec. Q in aV, 35-mm. S wave in V diminishing R wav amplitude from V to V large peaked upright T wa es in V, V
9	+	AF	+	+	Auricular fibrillation LAD parietal block QRS-T angle 180 degrees
10.	0	0	+	0	S-T ↓ in I II V, V

PVC: Premature ventricular contractions. AF Auricular fibrillation. LAD: Lef axis deviation.

not proved by the above-mentioned methods, they seem to fit the clinical criteria for this entity

The electrocardiograms were recorded on standard direct writing electrocardiographic instruments. The vectorcardiograms were recorded using the Frank lead system. The equipment and recording techniques used in this laboratory are described elsewhere.[6] The method of analysis is also described elsewhere [7] but in brief consists of the identification of three loops, Q R, and S. The Q loop is defined as the first abrupt change in the direction of the tracing within the first 20 milliseconds. The R loop is defined as the second major directional change, and the S loop as the last abrupt change in direction of the trac

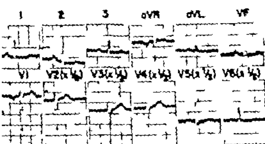


Fig. 1 Electrocardiogram in Case 1

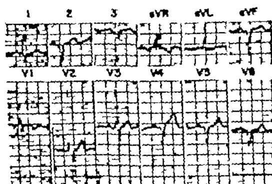


Fig. 2 Electrocardiogram in Case 2

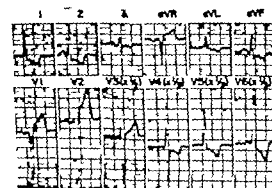


Fig. 3 Electrocardiogram in Case 3

ing usually occurring during the last 15 to 30 milliseconds. Straight lines from the origin to the apices of these loops are defined as the Q, R and S vectors. The R vector usually corresponds to the long axis of the tracing.

Results

Electrocardiograms. In all cases there was an abnormal electrocardiogram, but there was no uniformity in the type of abnormality seen. The data are summarized in Table II. Spontaneously occurring premature beats were unusual, occurring in only one of the suspected cases. This case also demonstrated auricular fibrillation.

ST-T abnormalities were present in all cases. These abnormalities ranged from a modest (0.5 to 1 mm.) S-T depression in Cases 1 and 10 to striking ST-T changes resembling left ventricular hypertrophy and strain in Cases 3, 7 and 9.

P wave abnormalities were common. P waves were large and broad in the limb leads with terminal negativity in Leads V_1 and V, which suggested left atrial enlargement and intra-atrial block.

QRS abnormalities were frequent. In one case (Case 2) electrocardiographic abnormalities consistent with myocardial infarction were seen. In several other cases abnormalities were seen which, although not diagnostic, were suggestive of myocardial infarction. These included (a) absence of an R wave in Lead V with a diminutive R in Lead V (Cases 5 and 7), (b) lack of progression of R wave size in right precordial leads (Cases 6 and 8), and (c) left axis deviation with a wide angle between initial and terminal forces (Case 9). Still others demonstrated large QRS amplitude in precordial leads which was consistent with left ventricular hypertrophy (Cases 1, 3, 5, 6, 8).

In Case 2, a 17-year-old boy, the striking electrocardiographic abnormality led to an initial clinical diagnosis of a previous myocardial infarct, despite the absence of any history suggestive of coronary artery disease. Because a congenital abnormality

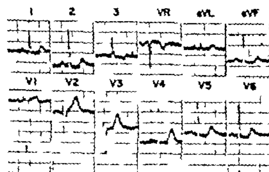


Fig. 4 Electrocardiogram in Case 4

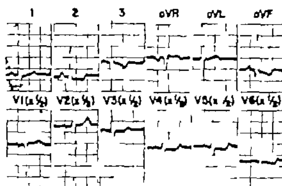


Fig 5 Electrocardiogram in Case 5

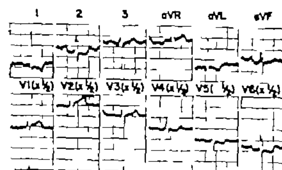


Fig 6 Electrocardiogram in Case 6

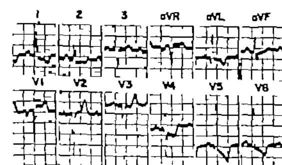


Fig 7 Electrocardiogram in Case 7

of the coronary vascular tree was suspected a coronary angiogram was obtained The major coronary vessels and their branches showed no variation from the normal vascular pattern

Vectorcardiograms In 9 of the 10 cases the 10 QRS loops were abnormal The abnormalities were most obvious in horizontal and sagittal views. Because of the varied character of the abnormalities and the small number of cases, statistical analysis was not carried out.

FRONTAL PLANE. In 4 cases (Cases 3-6) the initial forces moved immediately to the left *forming no well-defined Q loop This is* a nonspecific abnormality but one which is often seen in left ventricular hypertrophy [8] In one case (Case 7) there was a very large inferiorly directed Q loop which suggested a *high* lateral *infarct*. In another (Case 2) there was a very large superiorly directed Q loop which suggested an inferior or diaphragmatic myocardial infarct In the other cases (Cases 1 8 10) the Q loop had a normal position and size The mid forces (R vector) were to the left of the normal position in 3 cases

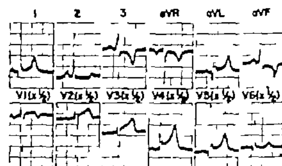


Fig 8 Electrocardiogram in Case 8.

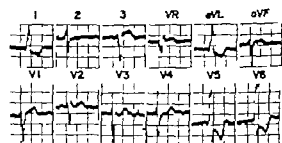


Fig 9 Electrocardiogram in Case 9

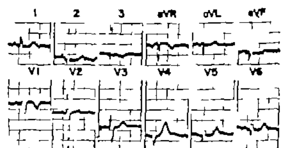
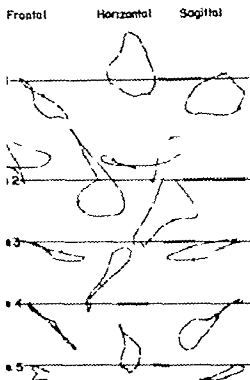


Fig. 10 Electrocardiogram in Case 10.



. *11* Vectorcardiograms in Cases 1-5. The frontal ps are viewed from the front, the horizontal ps from above, and the sagittal loops from the it side. Loops are interrupted at intervals of 1 second. The heavy portion of the line connect the origins of the three loops in given case icates the distance corresponding t 1 millivolt.

Cases 2 7 9) but in one (Case 10) the vector was directed to the right of the ormal range. Leftward shift of the mid rces of a moderate degree is commonly ncountered in left ventricular hype ophy In only 4 cases (Cases 2 5 6 9) as the S loop well defined. In the re mainder the efferent loop moved back to he point of origin without a distinct S oop. Absence of a well-defined S loop is lso a feature commonly encountered in eft ventricular hypertrophy

HORIZONTAL PLANE. As in the frontal plane, the abnormalities in the horizontal plane QRS loops were not consistent. In 2 cases (Cases 4 and 7) the initial forces assumed a clockwise direction moving posterior to the point of origin. This is a very abnormal otation of the initial loop and is usually *indicative of previous anterior myo*cardial infarction. In 2 cases (Cases 2 and 10) the initial forces were very large and anteriorly directed and were considered to be consistent with a previous posterodiaphragmatic myocardial infarct. In another (Case 8) the initial *Q loop* was unusual in that it moved posteriorly after a small, tight anterior loop failing to develop the usual *open Q loop*. Cases 3 5 and 6 showed an terior initial forces but without the rightward direction seen in most normal QRS loops. As in the frontal plane this immediate leftward direction of initial forces is a frequent finding in left ventricular hypertrophy

The mid forces were abnormally posterior in 7 of the 10 cases (Cases 3-7 8 10) Posterior position of mid forces is a common feature of left ventricular hypertrophy In keeping with this finding was the fact that Cases 3 4 5 6, 7 8 and 9 demonstrated an increased magnitude of the maximum QRS vector beyond the normal range Case 2 showed an abnormally anterior position of the R vector

The terminal forces were posterior in all cases. However in only Cases 2 and 3 were well-defined S loops seen

SAGITTAL PLANE In only one case (Case 1) was the sagittal view relatively normal

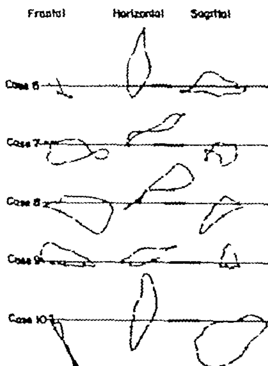


Fig. *12.* Vectorcardiograms in Cases 6-10.

in contour The rest demonstrated a variety of abnormalities.

The initial forces in 2 (Cases 2 and 10) were very large and anteriorly directed In another (Case 7) the initial forces failed to move anteriorly In another (Case 4) the rotation was abnormal the loop returning superior to the point of origin These abnormalities are all highly suggestive of previous myocardial infarction In 4 cases (Cases 3 5 8 9) the Q loop moved inferiorly a common finding in left ventricular hypertrophy In only 2 (Cases 1 and 6) did the initial forces appear to be relatively normal

The mid forces were posteriorly oriented Cases 3 5 6 7 and 9 were distinctly abnormal in this respect. Case 2 was difficult to characterize, and Cases 4 and 8 were within the normal range for mid force direction In 5 cases (Cases 4 5 6 8, 10) the amplitude of the maximum forces was increased above the normal range

Summary The QRS loops in 4 cases demonstrated abnormalities which were highly suggestive of previous infarction Two of the 4 (Cases 4 and 7) showed an abnormal direction of initial forces which was consistent with an anterior infarct In the other 2 cases (Cases 2 and 10) the abnormal initial forces suggested a previous posterior diaphragmatic myocardial infarct Another case (Case 9) showed left axis deviation and parietal block.

In 4 cases (Cases 3 5 6 8) the QRS loops demonstrated features that were suggestive of left ventricular hypertrophy with left ventricular conduction delay In each the electrical forces became posteriorly directed sooner than would be ordinarily expected Two manifested a clockwise tip of the QRS loop.

Discussion

The survey has shown that electrocardiographic and vectorcardiographic abnormalities are usually present with idiopathic hypertrophic subaortic stenosis, but that there is no uniform abnormality associated with the entity The abnormalities seen may resemble those due to left ventricular hypertrophy but may also resemble those due to myocardial infarction. Another entity can be added to the list of diagnoses to be considered when an electrocardiogram consistent with previous myocardial infarction is seen in the absence of a history of chest pain.

Thus, the original hypothesis, that the mechanical abnormality in hypertrophic subaortic stenosis might be related to an underlying abnormality in the sequence of activation is not supported by the data reported On the other hand the data do not rule out the possibility that an abnormal sequence of contraction unrelated to electrical events might be present or that an abnormal sequence could result from several conduction abnormalities of different character

The presence of electrocardiographic and vectorcardiographic abnormalities suggestive of previous myocardial infarction is of interest. None of the patients gave a history of a myocardial infarct, although a number had developed anginal pain with exertion Idiopathic myocardiopathy is known to simulate the electrocardiographic picture of myocardial infarction in the absence of significant coronary atherosclerosis.[9] This is also thought to be the case in this group of patients, but the possibility that coronary disease might be present in one or more of the group cannot be excluded

Summary

1 The electrocardiogram and vectorcardiogram are usually abnormal in cases of idiopathic hypertrophic aortic stenosis. ST T abnormalities are most frequently seen but P wave and QRS abnormalities are also seen The P wave abnormalities suggest left atrial enlargement and intra auricular block. The QRS abnormalities resemble those of left ventricular hypertrophy but may also mimic those of myocardial infarction in a variety of locations.

2. It is concluded that there is no uniform conduction abnormality associated with this lesion

Th technical assistance of M s. Elizabeth Naughton, M Frank London, nd Mr Albert Eaton is gratef lly cknowledged.

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Multiple pathways of conduction and reciprocal rhythm with interpolated ventricular premature systoles

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Beckley, W. Va.

Interpolated ventricular premature systoles (IVPS) were first described in man by Wenckebach.[1] The usual explanation for the ventricular systole which follows the IVPS is that it is a response to the regular pacemaking impulse from the S-A node. That this interpretation is often wrong is the conclusion of the present study. In half or more of unselected cases at least some of the systoles which follow the IVPS seem to be reciprocal beats, that is, they derive their stimulus from the IVPS. The impulse from the IVPS is conducted to or toward the atria and somewhere above the bifurcation of the bundle of His turns back to activate the ventricles again. The observations support the hypothesis of multiple pathways of conduction between atria and ventricles.[*] The multiple pathways provide a mechanism for reciprocal rhythm: the retrograde impulse from the IVPS travels along one path and the return impulse *travels back to the ventricles along another* path. That the ventricular systole which follows an IVPS in man may be due to reciprocal *rhythm has been recognized in* what were considered to be exceptional cases.[2,3] [1] The present study constitutes a systematic analysis of unselected cases of IVPS.

Material and methods

With simultaneous esophageal (E) and standard electrocardiograms,[17] 82 patients were studied. In 27 there were both IVPS and VPS followed by the more usual pause (referred to hereafter as *common* VPS). In 45 there were common VPS only. There were at least 5 IVPS in each case used for final analysis. A VPS was considered to be interpolated if the contour of the QRS which followed the IVPS was like that of the QRS of sinus origin; slight differences are not unusual and the illustrations show the variation considered permissible. Cases in which the QRS that followed a VPS was grossly different from the QRS of sinus origin were not included because of the problem of differentiation from two VPS in succession.

The terms preceding cycle and coupling are used. Preceding cycle is the time interval between the two activations *of a part of the myocardium preceding* the activation under study. Coupling is the time interval between the preceding activation and the activation under study.

VPS are usually recognized by their bizarre QRS configurations. Configuration alone, however, is not a certain *criterion* since the QRS of supraventricular origin

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also may be bizarre if ventricular systole occurs during a refractory phase of the ventricular myocardium. In a number of the cases there was evidence for the ventricular origin of the ectopic systoles aside from their bizarre QRS configuration The E leads, by clearly showing the absence of a P wave preceding the ectopic beat ruled out the possibility of atrial origin. In 10 of 19 cases with interpolated premature systoles and V A conduction additional evidence for differentiation from ectopic beats in the A V node or A V bundle consisted of (1) comparison of preceding cycles and couplings with the cycles and couplings of sinus beats and of atrial premature systoles followed by a normal QRS, and (2) fusion beats. Aberrant conduction in the ventricles is more likely with longer preceding cycles and shorter coupling In these 10 cases, cycles preceding the interpolated premature systoles were as short or shorter than cycles in the same tracing preceding (1) atrial premature systoles followed by a QRS like the QRS of sinus origin or (2) sinus beats and coupling intervals between the IVPS and the previous QRS were as long or longer than coupling intervals of QRS complexes initiated by atrial premature systoles or sinus beats. In 3 of the 10 cases, ectopic systoles sometimes occurred about the time when a QRS of supraventricular origin was expected and the resulting QRS suggested an intermediate contour resulting from fusion in the ventricles of activations of ventricular and supraventricular origins. If some ectopic beats which originate in the A V node or bundle can spread to the ventricles by way of pathways other than the usual one, even when the ventricular myocardium is not refractory[18] the above-mentioned criteria would not distinguish such beats from VPS

Among the patients with IVPS in whom V A conduction occurred some had heart disease and some did not. Some had received digitalis and some had not.

V-esophageal (VE) leads or/and bipolar esophageal (BE) leads[20,21] were obtained. The bipolar electrodes were two German silver rings 3 mm wide and 2 cm apart mounted on a rubber tube. When the electrode higher in the esophagus was electropositive with respect to the lower electrode, the deflection in the tracing was upward. In some cases the BE lead was recorded simultaneously with VE leads obtained from each of the electrodes of the BE lead according to the method of Copeland and associates.[9] The best level for recording esophageal P waves was determined in a given case by exploration. The electrocardiograms were recorded on 2-channel or 4-channel (Sanborn) direct recorders. The illustrated records were made at a paper speed of about 25 mm per second (smallest time mark = about 0 04 second) The measurements for Figs. 8 9 and 11 were made from the onsets of P and QRS in whichever of the simultaneous leads these were apparent earliest and all available measurements in a tracing were used

In the illustrations the numbers under VE indicate the location of the esophageal electrode in centimeters from the nares and the numbers under BE indicate the distance in centimeters from the nares of the mid-point between the two electrodes. The location of the electrode was not recorded for the tracings of Figs. 1 and 6 The illustrations are not retouched.

Observations and discussion

V-A Conduction The evidence for retrograde conduction to the atria after VPS has been presented In the E lead the retrograde P wave that follows the VPS differs in contour from the sinus P wave and may be premature with respect to the expected sinus rhythm. P waves occur which suggest fusion in the atria between retrograde activation and activation from the S-A node and support the interpretation of retrograde conduction Premature P waves which differ in contour from the sinus P wave are illustrated in Figs. 1 through 6 and 10 fusion P waves in Figs. 1 and 2 The interval from the retrograde P wave to the next sinus P wave is usually longer than the normal sinus P P interval (Figs. 1-3 5) but there are exceptions (Figs. 4 10) Apparently the VPS may occasionally accelerate the sinus rate by circulatory effects. Also if changes in sympathetic parasympathetic tone are the cause of the premature systole these changes may simultaneously accelerate the sinus rate for one or more cycles. These effects may counteract the usual effect of the retrograde atrial impulse. Circulatory effects of VPS on the sinus rate

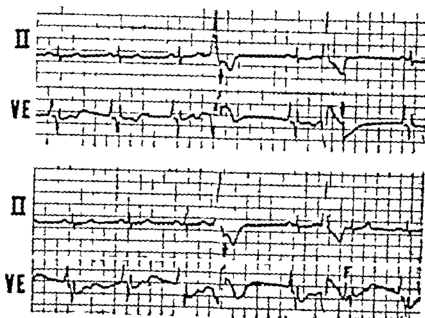


Fig. 1. Case 1. V-A conduction from VPS i... orders of magnitude of V-A conduction, IVPS followed by fusion P. Simultaneous Lead II and V-esophageal lead. Rapid V-A conduction after first VPS in each row. Slow V-A conduction after second VPS in each row. Arrows over retrograde P waves which differ in contour from the sinus P ... and are premature with respect to the expected sinus rhythm. The P which follows interpolated VPS in lower row is interpreted as result of fusion (*F*) of retrograde and sinus activations of the atria. The QRS which follows the IVPS, similar to the QRS of sinus origin, is interpreted as a reciprocal beat. Data in Fig. 8. The rapid V-A conduction is pictured diagrammatically in Fig. 7,g, the slow V-A conduction of the upper row in Fig. 7,f, and the IVPS ... Fig. 7,h.

were discussed by Engelmann.[22] In VF leads the direction of the retrograde P wave is often not opposite to that of the sinus P wave (Figs. 2, 3); sometimes it is (Figs. 4, 6). In selected BE leads the direction of the retrograde P wave is more likely to be opposite to that of the sinus P wave[11] (Figs. 2, 3, 5), especially in leads with sinus P waves such as those shown in Fig. 5. An inverted P wave in Lead II after the VPS may be discernible (after first VPS of each row in Fig. 1 and Figs. 2, 3, 5) or not (second VPS, upper row of Fig. 1 and Figs. 4, 6). P in Lead II may be upright (Fig. 4). The interpretation of A-V nodal rhythm in man with retrograde conduction to the atria and with an upright P in Lead II has previously been made.[23-25]

The interpretation of retrograde conduction to the atria from at least some of the VPS was made in 19 of the 27 cases with IVPS and in 31 of the 45 cases with common VPS only. The incidence is about the same. In the IVPS group the V-A conduction was recognizable in 12 of the 27 cases after both the IVPS and the common VPS, in 1 case only after the IVPS, and in 6 cases only after the common VPS. Among the cases with IVPS in which there seemed to be evidence for differentiation of the premature systoles from premature systoles of supraventricular origin (see *Material and Methods*), V-A conduction was recognizable after both the IVPS and the common VPS in 7, only after the IVPS in 1, and only after the common VPS in 2. Figs. 4 and 5 show retrograde P waves after both the IVPS and the common VPS. In Fig. 5 there is a retrograde P wave after the common VPS and one IVPS, but the P after another IVPS resembles the sinus P wave. In Fig. 6 there is a retrograde P wave after one IVPS, but the other IVPS is followed by a sinus P wave.

Trendelenburg[27] in frogs, and Rihl,[28] in mammals produced IVPS. VPS were conducted back to the atria. One of Trendelenburg's tracings shows one common VPS with retrograde conduction to the atria and one IVPS. Pan interpreted venous and arterial pulse tracings in man as showing retrograde conduction to the atria from

VPS. He believed that the ventricular systole which follows the IVPS could receive its stimulus from the retrograde atrial activation and he was possibly the first to use reciprocal rhythm as an explanation for IVPS. In pulse tracings it may be impossible to distinguish ventricular from A-V nodal premature systoles, and to distinguish an IVPS from two VPS in succession but Pan's Figure 16 may show VPS with retrograde conduction to the atria and his Figure 22 may show a retrograde P wave between an IVPS and the next systole

Cumenbauer[29] recorded electrocardiograms of VPS conducted to the atria in man One of his illustrations shows one common VPS followed by a retrograde P wave and one IVPS Retrograde conduction to the atria from VPS in man was considered to be rare until recent studies with esophageal leads.[29,30,2] It is significant that Lewis and Ashman were not satisfied that there was a good explanation for the infrequency with which V-A conduction was observed Lewis[14] wrote "The reason why many of the extrasystoles fail to propagate themselves to the auricle producing a retrograde beat remains mysterious. In some instances the retrograde impulse is calculated to coincide with the next natural auricular impulse, but this is not always the case" Ashman[31] wrote "One further point may be touched upon i.e. why is the retrograde impulse blocked? On this point we can say nothing Equally premature impulses in some hearts may pass back to the auricles. In my opinion the mystery and difficulty were simply technical the usual electrocardiographic leads may be inadequate to study V-A conduction Several authors hypothesized some degree of retrograde penetration of the impulse from

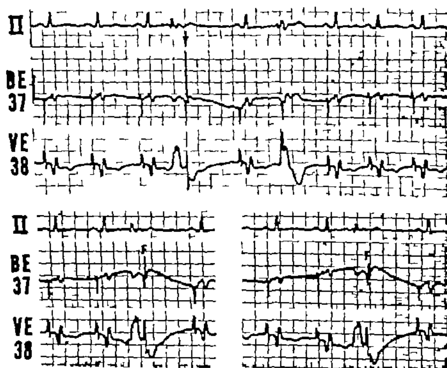


Fig 2 Case 2. V-A conduction from VPS, and fusion P waves supporting interpretation of V-A conduction. Simultaneous Lead II bipolar esophageal lead, and V-esophageal lead. *Upper* The QRS of the first VPS is followed by a retrograde P wave (*arrow*) different in contour from the sinus P wave, opposite in direction and premature with respect to expected sinus rhythm. The QRS of the second VPS starts immediately after the P of sinus origin—in the E leads the P is clearly seen superimposed on the QRS—and this VPS is not followed by a retrograde P wave *Lower* Two fusion P waves after VPS resulting from different degrees of fusion in the atria of activations of retrograde and S-A nodal origins. Rapid V-A conduction (*Upper*) pictured diagrammatically in Fig 7,g. Events after VPS in lower tracings pictured in Fig 7,h.

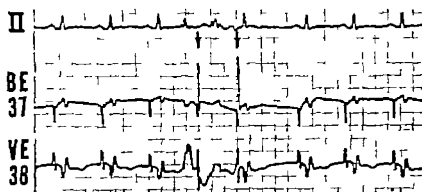


Fig. 3. Case 2. Two orders of magnitude of V-A conduction. Reciprocal rhythm after slow V-A conduction. Simultaneous Lead II, bipolar esophageal lead, and V-esophageal lead. Arrows over retrograde P waves. Possibly first retrograde P is result of fusion, activation of sinus origin making a small contribution to its contour. The second VPS is interpolated, and since it is followed by a retrograde P wave, the next QRS similar in contour to the QRS of sinus origin is interpreted as a reciprocal beat. Rapid V-A conduction pictured diagrammatically in Figs. 7,g and h; slow V-A conduction with reciprocal rhythm in Fig. 7,a.

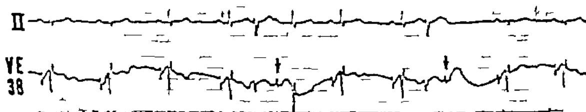


Fig. 4. Case 5. V-A conduction after IVPS and after common VPS. Simultaneous Lead II and V-esophageal lead. Retrograde P waves (arrows) different in contour from sinus P waves and premature with respect to sinus rhythm. The QRS which follows the IVPS resembles the QRS of sinus origin and is interpreted as a reciprocal beat. The events after the IVPS are pictured diagrammatically in Fig. 7,a, and those after the common VPS, in Fig. 7,f.

VPS to the A-V bundle,[illegible] to the tissues below the A-V node,[illegible] into the A-V node,[illegible] and to the atrionodal juncture.[illegible]

Reciprocal rhythm. When the impulse from the IVPS is conducted retrograde to the atria, the next QRS must be the result of reciprocal rhythm. In the same tracing there may be a retrograde P wave after the common VPS but not after the IVPS, or the IVPS may sometimes be followed by a retrograde or fusion P wave and sometimes by a sinus P wave (Figs. 5 and 6). The mechanism of an IVPS followed by retrograde conduction to the atria and reciprocal rhythm is illustrated in Fig. 7,a. The traditional concept of the IVPS followed by a sinus P wave is illustrated in Fig. 7,e. Since in the same tracing with the IVPS which is followed by a sinus P wave there may be other IVPS followed by retrograde P waves or common VPS followed by retrograde P waves, the possibility is suggested that reciprocal rhythm accounts also for at least some of the ventricular systoles which follow the IVPS which are followed by sinus P waves. This interpretation requires that the juncture between the retrograde and return pathways be located below the atria. In that case an atrial activation which results entirely from stimulation from the S-A node and produces a normal sinus P wave could occur between the IVPS and the next reciprocal ventricular systole. This mechanism is illustrated in Fig. 7,c. With slight differences in the times of sinus and retrograde impulses the mechanism in Fig. 7,d is hypothetically possible. It seems possible that more than one of the mechanisms, 7,c, 7,d and 7,e, might occur in the same tracing with slightly varying conditions.

Theoretically, mechanism 7,c might be recognizable if the interval from the P which follows the IVPS to the next QRS were shorter than the P-R which results

from normal A-V conduction although 7,c is not ruled out if the P-R following the IVPS is as long as or longer than the usual P-R, because of the possibility of conduction through tissue made partially refractory by the recent VPS (in Fig. 7 for example, the region immediately below the lower juncture of the pathways). Actually, however, the interval from the sinus P which followed the IVPS to the next QRS was as long as or longer than the usual P-R in the same tracing in the 25 cases in which some or all IVPS were followed by sinus P waves.

The durations of the intervals from the IVPS to the next QRS were measured. In 11 cases these intervals included a retrograde or fusion P wave, and there were three to many intervals for measurement. These intervals have been called reciprocation times.[7,14] Their ranges in the 11 cases were 0.45-0.46, 0.46-0.49, 0.47-0.52, 0.48-0.53

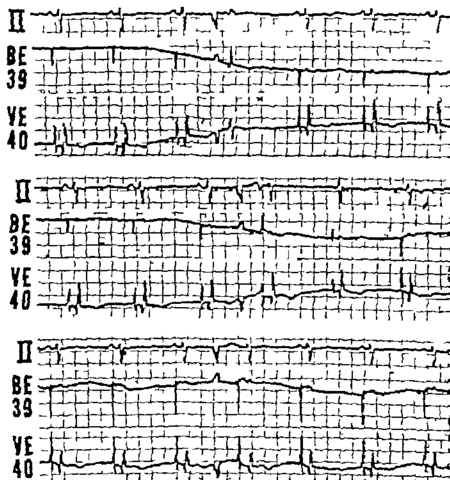


Fig. 5. IVPS sometimes conducted to the atria (*middle tracings*), sometimes not (*lower tracings*). Retrograde conduction to the atria after common VPS (*upper tracings*). Simultaneous Lead II, bipolar esophageal leads, and V-esophageal leads. The sinus P waves in the BE lead are large downward deflections; the retrograde P waves are large upward deflections. After the reciprocal beat in the middle tracings there is an A-V nodal escape beat with P preceding QRS; the P wave seems to be the result of fusion in the atria of the retrograde activation from the A-V node and sinus activation which occurs at about the same time. The breath was held during recording of the upper and middle tracings; this may account for the difference between the sinus P waves in these tracings and those in the lower tracings. The data in this case were inadequate to determine whether the V-A conduction times fell into distinct orders of magnitude as in other cases illustrated in Fig. 8. The events with the VPS of the upper tracings are pictured diagrammatically in Fig. 7,f or g, the middle tracings in Fig. 7,a, and the lower tracings in Fig. 7,c, d, or

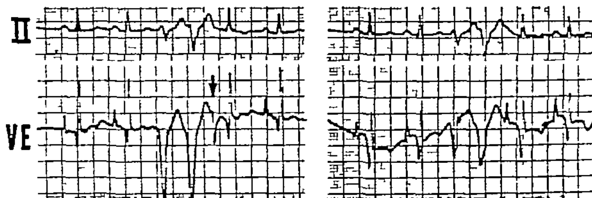


Fig. 6. IVPS sometimes conducted t tria (l ft) somet mes not (right). Simultaneous Lead II and V-esophageal lead. Arrow over retrograde P wa e. The duration of the cycle preced ng the first VPS and the coupling of this VPS to the preceding sinus beat are about the same in both sets of tracings. The interval between the two VPS is little horter in the tracings on the right. The events after the IVPS on the left are illustrated diagrammatically in Fig. 7,a. Those after the IVPS on the right may be explained by the diagrams of Fig. 7,c d or . The difference between the QRS complexes in the two set of esophageal tracings is probably the result of a shift in position of the esophageal t be.

0 46-0 52 0 46-0 58 0 48-0 60 0 44-0 57 0 53-0 73 (0.58-0 67 and 0 74-0 80) and (0.56-0 60 and 0.58-0 67) second. The values in parentheses are for Cases 5 and 6 (Figs. 10 and 11) discussed further on in which there were two orders of magnitude of the intervals from the retrograde P wave to the next QRS. In 6 of the 11 cases there were also three or more IVPS which were followed by sinus P waves in 5 all intervals from these IVPS to the next QRS fell within the range of the reciprocation times in the same tracing. In one case a number of the intervals which included sinus P waves fell within the range of the reciprocation times, but others were up to 0 13 second beyond the range.

The reciprocation times were found in some studies[4, 13,14,15] to vary not more than 0 06 second in a given tracing. The constancy of the interval was used as evidence of reciprocal rhythm when the interval did not include a retrograde P wave, the explanation in such cases being that already discussed namely that the reciprocal mechanism was below the atria and within the A V node. In the present study the range of reciprocation times in some of the cases is no greater than that observed in the afore-mentioned studies. In other cases, however the variation is greater corresponding with my previous observations.[3] A constant reciprocation time may be related to stable conditions with narrow ranges of retrograde and return conduction times. When the V A conduction time is more variable (Fig 8) possibly because of variations in the coupling intervals of the IVPS or the durations of the cycles preceding the IVPS[3] (Fig 9) or other factors, and when the return conduction time is more variable[4] (Figs. 10 11) then more variability may be expected in the reciprocation time.

That the intervals which included a sinus P wave fell within the range of the reciprocation times in 5 of 6 cases in which the comparison could be made is at least consistent with the thesis that during some of these intervals, too reciprocal rhythm may have occurred by way of an infra atrial probably A V nodal mechanism.

In the 6 cases in which IVPS followed by a sinus P wave could be compared in the same tracing with IVPS which were followed by a retrograde P wave the coupling of the IVPS was in about the same range for both types of IVPS.

V A conduction is demonstrable as frequently in cases with common VPS only as in cases with IVPS judging from the data presented in the preceding section. The occurrence or absence of reciprocal rhythm after VPS cannot therefore be related solely to whether V A conduction is demonstrable or not. Rather V A conduction should be considered the prevalent basis for reciprocal rhythm the reciprocal rhythm may or may

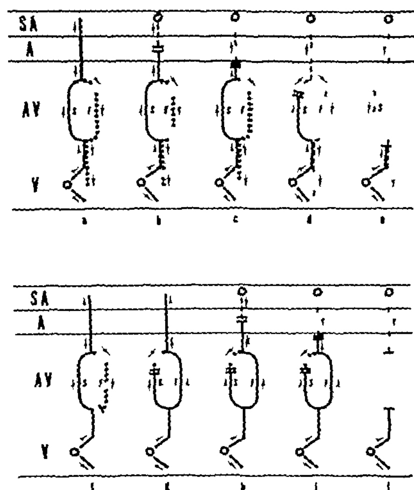


Fig. 7 Hypothetical diagrams of some of the events that may follow VPS two pathw ys of conduction are assumed. *SA* S-A node. *A* Atrium. *AV* A-V node. *V* Ventricle. *Stars* Sites of origin of impulses in the ventricular ectopic focus and in the S-A node the onset of the VPS in all instances precedes the onset of sinus activation, and the sinus impulse is the one immediately following the VPS. *S* Slow pathway *F* Fast pathway Single line across the direction of impulse (f j) indicates block because of ref actoriness. Double line cross the direction of impulse (b c, d g, h) indicates block because of interference at the meeting of two impulses from opposite directions. *Solid lines* Retrograde conduction from VPS *Lines of circular dots* Return activ tion starting at juncture of retrograde and return pathways. *Lines of dashes* Conduction from S-A node. A dividing line is not show bet een the A-V node and entricle although the evidence indicates a lower juncture of the pathways above the bifurcation of the bundle of His, it is not possible to say whether this juncture is in the A-V node proper or in the bundle below the A-V node. The reasons for placing the pper juncture of the pathways in the A-V node are discussed in the text *b* and show IVPS due to reciprocal rhythm with different atrial mechanisms. *d* show IVPS, the beat following the VPS resulting from the sinus impulse. show IVPS block of the retrograde impulse in both path ay in the A-V node with recovery of the slow pathway by the time the sinus impulse eaches the A-V node, and conduction to the entricles of the sinus impulse. *f* shows A-V conduction by the slow pathway th block of the return impulse due t refractoriness of part of the return pathway *g*, *h*, *i* show retrograde conduction simultaneousl along both pathways, with resultant rapid A-V conduction, with meeting of the retrograde and return impulses in the slow pathway and with different trial mechanisms. *j* shows block in the A-V node of the retrograde impulse in both path) and subsequent block in the A-V node of the sinu impulse Not all possibilities are shown For example, the A-V conduction in may occur simultaneously along both pa hway (see *g*) f *f* the trial mechanisms show in *h* and *i* may occur and the eturn impulse ma be blocked t any point in the fast pathw y The interconnections bet een the pathway may be more complex, and there may be more terconnections. is illustrated in Figs. 3 4 5 nd 10 *b* in Fig. 1 5 Figs. 5 and 6 the IVPS followed by sinus P wave may be due *to d*, *or e*. its the traditional concept of IVPS (omitting the hypothesis of multiple pathways). *f* is illustrated in Figs. 1 and 4; *g* in Figs. 1 and 2; *h* in Fig. 2. *j* is the traditional concept of common VPS followed by sinus P wa e.

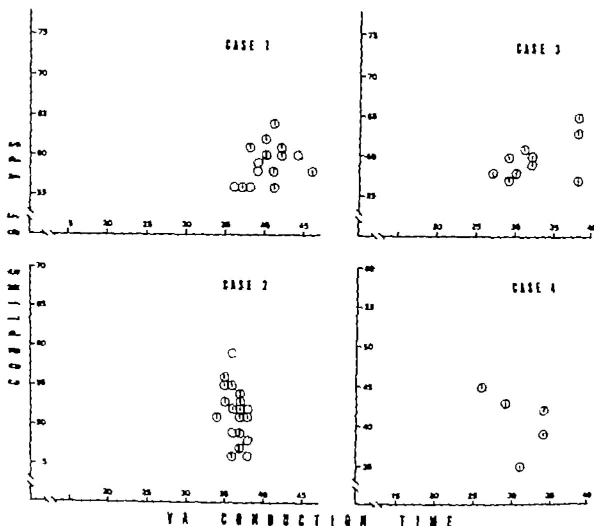


Fig. 8. Two orders of magnitude of V-A conduction time, evidence for two pathways. Relation of V-A conduction time to coupling interval of VPS. Numbers along ordinates and abscissae = hundredths of second. Plotted numbers = number of observations at the plotted point. Numbers enclosed in circles = IVPS; other numbers = common VPS. In each case the VPS are from a single focus, determined from the configuration of QRS. In Cases 1 and 3 the VPS followed a sinus beat, and the coupling interval was measured from the P wave preceding the VPS to the VPS. In Cases 2 and 4 the VPS followed another VPS, and the coupling interval was measured between the two VPS. The V-A conduction times (sec.) are: Case 1—0.14 to 0.22 and 0.31 to 0.46; Case 2—0.21 to 0.24 and 0.34 to 0.38; Case 3—0.15 to 0.20 and 0.27 to 0.38; Case 4—0.13 to 0.18 and 0.23 to 0.34. The larger order of magnitudes of V-A conduction time is more likely when the VPS occurs early.

not occur, depending on other conditions.

In man, IVPS due to reciprocal rhythm were described by Pan, Levin, Langendorf, Katz and Simon,[8] Malinow and Langendorf,[9] Grau and Gouaux,[11] Mesquita,[12] Kistin and Landowne,[3] Schott,[13] Pick,[14] Scherf and Schott,[15] and Katz and Pick.[6] I[3] attempted to analyze the conditions for the occurrence of reciprocal rhythm after IVPS. The analysis of a case of IVPS due to reciprocal rhythm by Langendorf, Katz and Simon presents clearly the concepts: (1) the retrograde impulse may extend varying distances, reaching the A-V node but not the atria, or reaching the atria to fuse with the activation from the S-A node, or involving the atria completely, and (2) a small distance and time may determine whether the bypass for reciprocal rhythm is reached first by the retrograde impulse or by the sinus impulse, so that in the same tracing some IVPS will probably be due to reciprocal rhythm and some not.

Scherf and Shookhoff[16] studied reciprocal beats in dogs after induced VPS and after an induced atrial premature systole. Moe

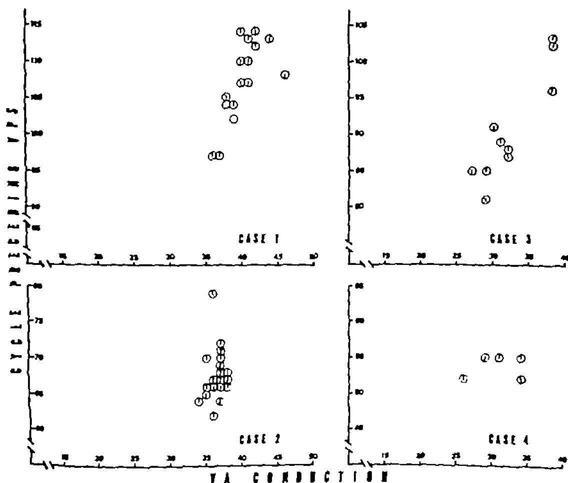


Fig. 9. Two orders of magnitude of V-A conduction time: evidence for two pathways. Relation of V-A conduction time to the duration of the cardiac cycle preceding the VPS. The cases are the same as in Fig. 8. The VPS in Case 3 followed a sinus cycle measured between the P waves. Some of the VPS in Case 1 followed a sinus cycle measured between the P waves. Others followed a sinus beat which was preceded by a VPS with retrograde conduction to the atria (Fig. 1). The cycle preceding these VPS was taken as the interval between the preceding retrograde P wave and the immediately preceding sinus P wave. The VPS in Cases 2 and 4 were the second of a pair of VPS, and the preceding cycle was measured from the sinus P wave preceding the first VPS to the first VPS. The larger order of magnitudes of V-A conduction occurs after both long cycles (Cases 1 and 2) and after short cycles (Case 4). Discussed in text.

Preston, and Burlington observed both ventricular and atrial echoes (reciprocal beats) in dogs and Rosenblueth observed ventricular echoes. Dohi and associates[17] produced ventricular and atrial reciprocal beats in dogs whose conduction systems were depressed by digitalis, quinidine or procaine amide. Atrial reciprocal beats were far more difficult to induce than ventricular reciprocal beats. These authors found that IVPS which were followed by a sinus P wave were coupled closer to the previous beat than were IVPS which were followed by retrograde P waves and reciprocal rhythm. Their interpretation is that the retrograde impulse is blocked after the IVPS which is followed by a sinus P and they do not consider the possibility of reciprocal rhythm with such IVPS. Two possibly significant differences should be noted between these experimental studies and the clinical studies under discussion. (1) The wide range of couplings so easily produced in the experimental studies was usually not observed in the patients. It has already been noted that in the cases under discus-

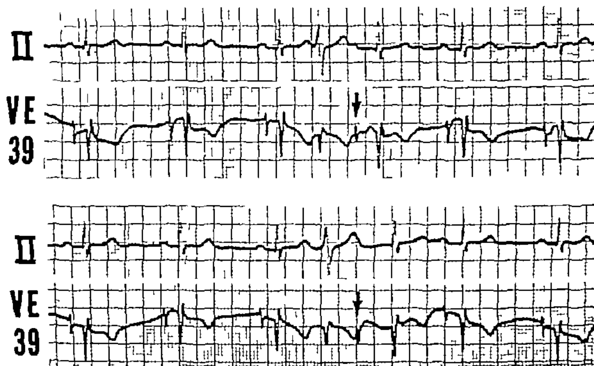


Fig 10 Case 5 Two orders of magnitude of P′ R P′ R is the interval from the retrograde or fusion P wave which follows the interpolated VPS to the next QRS. Simultaneous Lead II and V-esophageal lead. Short P′ R in upper tracings. Long P′ R in lower tracings. P′ in upper tracings is premature with respect to sinus rhythm. P′ in lower tracings occurs about the time of expected sinus P wave and may be a result of fusion in the atria of retrograde and sinus activations. Data in Fig 11

sion the coupling of the IVPS followed by a sinus P wave was about the same as the coupling of IVPS in the same tracing followed by retrograde P waves and reciprocal rhythm (2) A number of the patients with IVPS had no heart disease and had been taking no depressing drugs.

Multiple pathways of conduction.

MULTIPLE PATHWAYS FOR V A CONDUCTION In 4 of the 27 cases with IVPS the V A conduction times occurred in two separate orders of magnitude Case 1—0 14 to 0 22 and 0 31 to 0 46 second Case 2—0 21 to 0.24 and 0.34 to 0.38 second Case 3—0 15 to 0.20 and 0 27 to 0.38 second and Case 4—0.13 to 0 18 and 0 23 to 0.34 second (Fig 8) The interpretation is that the different orders of magnitude represent conduction along different pathways.

The order of larger magnitudes of V A conduction is more likely to occur when the VPS is early (short coupling) (Fig 8) These observations are like those previously made and are interpreted to mean that the refractoriness of a slower conducting path way is briefer than that of a fast-conducting pathway [3,4] Suppose that during the beat preceding the VPS both pathways are activated as illustrated in *g* *h* or *i* of Fig 7 (A diagram similar to Fig 7,*g* may be used to represent A V conduction from ordinary sinus beats along both pathways, with interference in the slow path between the fast and slowly traveling impulses.) Suppose also that the slow pathway recovers sooner A VPS occurring early enough would then find the slow-conducting pathway responsive when the fast one is still refractory The recovery of the fast path during the retrograde conduction along the slow path provides a possible return path and a mechanism for reciprocal rhythm and IVPS (Fig 7)

An additional factor which may determine slow V A conduction at a time when the fast pathway is refractory is the duration of the cardiac cycle preceding the VPS (Fig 9) Response of the slow pathway at a time when the fast pathway is refractory apparently occurs either after the longest

cycles in a given case or after the shortest cycles. In Cases 1 and 2, V A conduction along the slower pathway was more likely after long preceding cycles. This corresponds with previous observations.[3] During the increased refractoriness that results from the longer preceding cycle[18] there is apparently more likelihood of detecting responsiveness of the slow pathway at a time when the faster pathway is still refractory In Case 1 many equally early VPS occurred after cardiac cycles of varying durations, but only after VPS that followed cycles longer than 0 96 second did the slower V A conduction occur These effects of the duration of the preceding cardiac cycle and the coupling interval on the selection of the order of magnitude of V A conduction are concisely illustrated in Table I There were twelve common VPS in Case 1 like the second VPS in the upper tracings of Fig 1 VPS which followed a sinus beat which in turn followed another VPS When the preceding cycles were 1 03 to 1 16 seconds and the coupling intervals were 0.59 to 0 62 second the slower V A conduction occurred with conduction times of 0.31 to 0.36 second. Twice after cycles of similar duration there were longer coupling intervals of 0 64 and 0 65 second and the faster V A conduction occurred with conduction times of 0 15 and 0 17 second Once at a coupling interval of 0 60 second a VPS followed an exceptionally short cycle of 0 63 second and the faster V A conduction occurred with a conduction time of 0 14 second

In Case 2, all the VPS which were followed by the slower V A conduction occurred both early (Fig 8) and after longer cycles (Fig 9) the coupling intervals were 0.46 to 0.59 second the preceding cycles were 0.62 to 0 9 second and the V A conduction times were 0 34 to 0 38 second. Two VPS occurred after cycles of 0 65 and 0 67 second, but at longer coupling intervals of 0.62 and 0 69 second and the faster V A conduction occurred with conduction times of 0 22 and 0 24 second. Four VPS at coupling intervals of 0.65 to 0 70 second and after cycles of 0.59 to 0 61 second were followed by the faster V A conduction with conduction times of 0.21 to 0.22 second In Case 3 the influence of the duration of the preceding cardiac cycle could not be demonstrated the slower V A conductions followed cycles in about the same range as those which were followed by the faster V A conductions.

The data of Case 4 suggest the possibility that after extremely short cycles the slow pathway may sometimes respond when the fast one does not. The cycles in this case are the shortest plotted in Fig. 9 The VPS under consideration in Case 4 are the second of a pair of VPS so that the preceding cycle is an interval between a sinus beat and the first VPS. Dohi and associates[17] induced a pair of VPS in dogs, keeping the interval between the two VPS about the same and varying the interval between the first VPS and the preceding sinus beat. They found, as in Case 4, that at shorter intervals between the sinus beat and the first VPS the V A conduction after the second VPS might

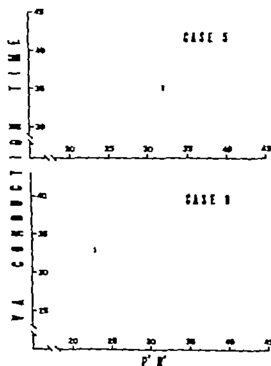


Fig 11 T o orders of magnitude of P' R evidence for two pathways of conduction in the A-V direction. Numbers along ordinates and abscissas = hundredths of second. Plotted numbers = numbers of observations of each plotted point. Relation of P'-R to V A conduction time. The ranges of P' R are (sec.): Case 5—0 23 to 0.32 and 0.41 to 0.45 Case 6—0.19 to 0.24 and 0 31 to 0.36. The order of larger magnitudes of P' R occurs after faster V A conduction.

Table I. Relation of the order of magnitude of V-A conduction time to the duration of the cardiac cycle preceding the VPS and the coupling interval of the VPS

Cycle preceding VPS (sec.)	Coupling of VPS (sec.)	V-A conduction time (sec.)
1.15	0.59	0.32
1.1	0.62	0.35
1.16	0.59	0.32
1.11	0.62	0.36
1.13	0.59	0.31
1.10	0.61	0.33
1.03	0.60	0.31
1.03	0.60	0.33
1.05	0.59	0.31
1.15	0.65	0.15
1.04	0.64	0.17
0.63	0.60	0.14

Data for the twelve VPS in Case 1 like the second VPS in the upper row of Fig. 1. Discussed in text.

be longer and might be followed by a reciprocal beat. It may be that at the shortest cycles another factor appears to disturb the direct relationship between the durations of cardiac cycle and subsequent refractory period: the beat which determines the duration of the cycle (in this case the first VPS) may occur so early that it finds the conducting tissues in the partially refractory phase produced by the previous beat. The subsequent beat (in this case the second VPS) may then encounter increased refractoriness of the conducting tissues that results from repeated activation during incomplete recovery. Under these circumstances the second VPS may be so timed as to find the slow pathway recovered at a time when the fast pathway is still refractory.

In the 31 cases with common VPS only and with retrograde conduction to the atria after the VPS, the ranges of V-A conduction times were narrow and there was no evidence of different orders of magnitude.

The existence of two orders of magnitude of V-A conduction and retrograde conduction by way of the slow path does not necessitate reciprocal rhythm; some part of the return path may be refractory when the impulse that results from V-A conduction reaches it (Fig. 7,f). Within the orders of larger magnitudes a number of the V-A conductions in Case 1, one in Case 3, and one in Case 4 were not followed by reciprocal rhythm (Fig. 8). These were the fastest V-A conductions within the orders of larger magnitudes, and presumably the retrograde impulse reached the return pathway before it had recovered.

Separate orders of magnitude of V-A conduction were previously observed[1,2] and explained by different conduction pathways. Decherd and Ruskin[14] gave a similar explanation for their observations in A-V nodal rhythm. Fleischmann[15] observed significant change in the QRS-to-retrograde-P intervals in successive beats of A-V nodal rhythm and attributed this to multiple conduction mechanisms. Experimental evidence for two pathways in dogs has been presented by Moe and associates[4] and by Rosenblueth.[4] Study of individual A-V nodal fibers in experimental animals by Hoffman and Cranefield[17] has not revealed fibers with different conduction properties that might characterize separate pathways, but these authors concede that some of the observations in support of the hypothesis of dual pathways cannot be explained by known properties of individual A-V nodal fibers.

The multiple pathways are considered here as normal constituents of the conduction system. This is discussed in the section *The Nature of the Pathways*. Reciprocal rhythm occurs also as a result of other mechanisms. In some cases of A-V nodal rhythm, for example, there is progressive prolongation of retrograde conduction time as a result of the Wenckebach phenomenon, and when the conduction time is sufficiently long, reciprocal rhythm occurs. In such cases it is necessary only to assume some variability of the impaired conduction in different fibers. While conduction is proceeding slowly in some fibers, it may be blocked in others; if the latter fibers recover before the retrograde conduction is completed, they may serve as a return or reciprocal pathway.

MULTIPLE PATHWAYS FOR A-V CONDUCTION. In 2 cases with IVPS the intervals from the retrograde P wave to the following QRS (P'-R) occurred in two orders of magnitude (Figs. 10, 11). Case 5—0.23 to 0.32

and 0.41 to 0.45 second. Case 6—0.19 to 0.24 and 0.31 to 0.36 second. These were cases other than those with two orders of magnitude of V-A conduction. The occurrence of P' R in separate orders of magnitude after IVPS is a new observation in so far as I can determine. It indicates that conduction may occur by multiple pathways in the A-V direction as well as in the V-A direction.

The P' R times were plotted against the V-A conduction times which resulted from the IVPS, the coupling intervals of the IVPS, the time of occurrence of P' in the cardiac cycle, and the duration of the cardiac cycle preceding the IVPS. The one relationship that stands out clearly in both cases is that to the V-A conduction time (Fig. 11): the order of larger magnitudes of P' R occurs after faster V-A conductions. In Case 5 there is no relationship of the order of magnitude of P' R to the coupling interval of the IVPS, the time of occurrence of P' in the cardiac cycle, or the duration of the cardiac cycle preceding the IVPS. In Case 6 there is some tendency for the larger order of magnitudes of P' R to occur (1) with longer coupling intervals of the IVPS, (2) with a P' which occurs earlier in the cycle, and (3) with shorter cardiac cycles preceding the IVPS. These relations are not so clear as is the relation of P' R to V-A conduction time, and they may be secondary manifestations of the relation of V-A conduction time to P' R. The secondary relations may derive from the possible inverse relationship of V-A conduction times to the coupling interval of the VPS and the direct relationship of V-A conduction times to the duration of the preceding cardiac cycle[4]; the time of occurrence of P' in the cardiac cycle depends on the speed of V-A conduction.

The magnitudes and the separations between the orders of magnitude of P' R are similar to those observed for V-A conduction time. The configurations of QRS after the short and long P' R intervals are similar and resemble that of the QRS of sinus origin.

The relation of the order of magnitude of P' R to the V-A conduction time suggests that the interval between the stimulation of some structure during the retrograde conduction and its stimulation again during return conduction determines the slow or fast response during return activation. Suppose that in such a structure—part of the A-V node or bundle of His—retrograde conduction activates both slow and fast pathways; the return activation may reach this same structure again at a time when the slow pathway has recovered and responds, whereas the fast pathway is still refractory. The interval between retrograde and return activations of such a structure cannot be measured in the electrocardiogram, but the V-A conduction time may be a useful index; other things being equal, the interval should be briefer with rapid V-A conduction and longer with slow V-A conduction.

The two orders of magnitude of P' R pose problems which require further study. Are the slow and fast V-A paths the same as the slow and fast A-V paths? If the V-A conduction in Cases 5 and 6 is by way of a slow pathway, is the availability of two return pathways evidence of more than two possible pathways to start with? The concept of Moe and associates, of two main pathways with several possible interconnections or crossovers at different levels is, in fact, a concept of more than two simple pathways and would fit the data of Cases 5 and 6. One other hypothetical possibility may be mentioned because it too assumes only a modification of the concept of two main pathways. Suppose there are regions of different responsiveness in the retrograde course between ventricle and atria, each with significant influence on the over-all conduction time. During V-A conduction, some region *A* may conduct the impulse along both pathways, whereas in another region *B* only the slow response may be available. The over-all V-A conduction may be delayed by *B*. During return activation, conduction may now occur in *B* along the fast pathway, whereas in *A* the response may be slow or fast, depending on the interval between the retrograde and return activation of *A*. The over-all conduction time during return activation would be determined by *A*.

Greatly prolonged P-R intervals and abrupt changes to considerably shorter intervals have sometimes been observed in individuals who had no heart disease. Manning and Stewart[44] attributed the changes in their case to conduction along different

pathways. The changes in P R occurred spontaneously,[42,44, 4] after exercise,[4,42,44-46] after atropine,[42, 47] and after change from recumbent to upright posture.[4, 44,47,48] Variations of P R in an individual were observed from 0.40 to 0.20 second,[46] 0.32 to 0.14 second,[42] 0.72 to 0.32 second,[44] 0.40 to 0.18 second,[42] 0.39 to 0.15 second,[46] 0.40 to 0.16 second, and 0.41 to 0.20 second.[48] Similar changes have been observed in individuals with heart disease and individuals whose cardiovascular normality was uncertain or not clearly described.[49-51] The differences in P R are, in general, similar to those observed in the present study between the orders of magnitude of V A conduction times and P′ R.

In relation to IVPS there are two possibly pertinent reports. Katz, Langendorf, and Cole[52] observed unusually long P R intervals after IVPS. The longest P R intervals were more likely to occur when the interval between the VPS and P was shortest, and the shortest P R times were more likely to occur when this interval was longest, but there was an unexplained wide range of P R times for other intervals. When P occurred 0.09 to 0.15 second after the VPS there was sometimes no conduction, three times a P R of 0.68 to 0.78 second, and twice a P R of 0.38 to 0.42 second. Spang[53] illustrates a tracing with IVPS in which seven following P R intervals are 0.17 to 0.22 second, one is 0.34 second, and one is 0.40 second.

Gertz and associates[49] and Segers[51] explained differences in P R by conduction along different pathways, but in these cases there were 2:1 and higher degrees of A V block. Since block alone may account for the P R differences, the evidence for multiple pathways is inconclusive. The possibility of reciprocal rhythm with alternating A V pathways after A V nodal beats was considered in one case by Scherf and Schott.[14] Alternating A V conduction time was reviewed and analyzed by Langendorf,[52] and explanations other than multiple pathways were given.

The nature of the pathways. A tentative physiologic and anatomic concept of the pathways may be ventured on the basis of the limited evidence. The pathways have different refractory periods. They transmit the impulse with significantly different conduction times—why is not known, but as Moe et al.[4] have pointed out, the possibilities are (1) different conduction velocities, (2) different lengths of the pathways, or (3) different interposed regions of block.

The reason for believing that the fast return pathway joins the normal A V pathway somewhere above the bifurcation of the bundle of His is that the contour of the QRS which follows the IVPS is similar to that of sinus origin in the present study. It should be noted that by selection the IVPS in the cases studied was followed by a QRS like that of sinus origin; this was to avoid the problem of distinguishing a second VPS from a reciprocal beat with aberrant conduction. From this study, therefore, it is not possible to say whether the return path may in other cases deviate from the normal A V pathway, at least for a distance into the ventricle.

The reason for believing that both fast conducting and slow-conducting A V pathways join above the bifurcation of the bundle of His is that the configuration of the QRS after both the short and long P′ R times in Cases 5 and 6 of this study is the same and resembles the configuration of the QRS of sinus origin. If the cases of different orders of magnitude of P R cited from the literature are evidence for multiple pathways of conduction, then these also indicate a juncture between fast and slow A V paths above the division of the bundle of His, since the QRS contour in most of the illustrated cases is the same after fast or slow conduction.[44, 4-48] Slight changes that involve the presence or absence of a minute Q or S after the different conduction times[42,44] may possibly be explained by changes associated with the exercise and atropine used to bring out the P R differences; in these cases also the similarity of the contour of the main part of QRS supports the hypothesis of a juncture of A V pathways above the bifurcation of the A V bundle. Moe and associates[4] believe that in dogs, the slow A V pathway may be separate from the normal A V pathway for some distance into the ventricle, since atrial stimulation at a time when this path was presumably responsive produced QRS complexes which differed in contour from the QRS which resulted from A V conduction by way of the fast path.

Scherf and Shookhoff[36] concluded from studies in dogs that the site for the juncture between retrograde and return impulses after IVPS may be below the atria proba bly in the A V node. Supporting evidence in man was presented by Cutts[31] Levin Langendorf Katz and Simon Pick and Langendorf[14] and Fleischmann[36] Further evidence for this view has been presented in this study of IVPS Rosenblueth hy pothesizes that the juncture of retrograde and reciprocal paths is in the atria. He believes that retrograde conduction occurs by way of the A V node but that return activation occurs from the atria through a synapse with the bundle of His, which by passes the A V node and which conducts only in the A V direction Rosenblueth s criticism of a reciprocal mechanism within the A V node does not include considera tion of possible separate fast and slow pathways.

The uncovering of two pathways in 6 of the 27 unselected cases of IVPS suggests that these pathways are normal constitu ents of the conduction system of man recognizable under the special conditions discussed In 3 of the 6 patients in whom the two pathways were ecognized there was no evidence of heart disease or at most some questionable signs, and the standard 12 lead electrocardiograms were normal F ve of the 6 had not been taking dig talis or other drugs which might affect conduction That the separate pathways were not ecognized more frequently may be simply because the special conditions necessary for recognition do not occur more frequently in clinical electrocardiograms.

Whether the slow and fast V A paths in man are identical in their entire course w th the corresponding A V paths equires fur ther study There is nothing inconsistent in the present study w th the v ew that they are and they have thus been tentatively represented in Fig 7

Since I have in one case observed data consistent w th three orders of magn tude of V A conduction I prefer to speak of multiple rather than dual pathways. Since the pathways anastomose and since con duction seems to occur readily in both the A V and V A directions, the conduction by way of the faster pathways will discharge the slower ones (F g 7) and only the fast est conduction will be recognized. A second slower pathway can be recognized only under the unusual circumstance that it responds at a time when a faster path does not a third pathway can be recognized only under the probably still more unusual circumstance that it responds when two faster pathways do not, etc It is not sur prising that the second or dual pathway may be recognized more frequently than third and possibly higher-order pathways.

James[36] has suggested an anatomic basis for multiple pathways of conduction in the connections of the atrial fibers to the A V node connections to the upper part of the node as well as to the lower part by way of what he terms bypass fibers.

Summary and conclusions

Analysis of simultaneous esophageal and standard electrocardiograms of 82 patients with ventricular premature systoles (VPS) provides evidence for multiple pathways of conduction and the frequent occurrence of reciprocal rhythm

In half or more of unselected cases w th interpolated VPS at least some ventricular systoles following the interpolated VPS are reciprocal beats, receiving their stimulus from the VPS and not, as is usually believed from the S-A node. Ventriculoatrial (V A) conduction occurs in 19 of the 27 cases with both interpolated and noninterpolated VPS and in 31 of the 45 cases w th nointer polated VPS only V A conduction the basis for reciprocal rhythm is equally f e quent in both groups. The other observed determining factors for reciprocal rhythm are the V A conduction time the prema turity of the VPS and the duration of the cardiac cycle preceding the VPS In 6 of the 27 cases with interpolated VPS there are two separate orders of magnitude of con duction times, evidence for different path ways. In 4 cases different magnitudes are demonstrable for V A conduction In 2 other cases they are demonstrable in the A V direction a new observation with n terpolated VPS The different pathways a e probably the mechanism for the eciprocal rhythm.

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Phonocardiographic and electrocardiographic studies in normal newborn infants

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Cardiac auscultation of the newborn infant[1-3] and electrocardiograms recorded during the early hours of life have provided important information concerning the state of the circulation. Patency of the ductus arteriosus of infants has been inferred by Burnard[1] from his phonocardiographic studies of normal newborn infants and those with asphyxia and has been shown by Rudolph[3] by cardiac catheterization of newborn infants with the respiratory distress syndrome. Braudo[4] found that heart murmurs were frequently present in a series of normal newborn infants: continuous murmurs were noted in 14 per cent, crescendo systolic murmurs in 5 per cent, ejection systolic murmurs in 56 per cent, and loud early systolic murmurs rarely. The great variation in the incidence of heart murmurs in newborn infants in different studies,[5-] from Lyon's[6] low figure of 1.9 per cent to the over-all incidence of 60 per cent observed by Braudo has not been explained.

The most striking electrocardiographic change that has been observed is the shift in the T-wave vector to the left and posteriorly during the first 48 hours.[1]

The purpose of the present study was to obtain objective auscultatory data through the use of standard phonocardiographic techniques and to correlate these observations with precordial electrocardiograms recorded simultaneously. The influences of variations in obstetrical management on the phonocardiograms and electrocardiograms were evaluated. The findings will be discussed in relation to the known physiologic changes at birth.

Materials and methods

Group A. Studied by electrocardiography and standard phonocardiography. Sixty-one normal white and Negro term newborn infants were studied. These infants were selected at random from the total newborn population at the North Carolina Memorial Hospital during July and August of 1959 and 1960. Excluded from the study were all infants who weighed less than 5½ pounds, all babies of known infected mothers, all babies of mothers whose membranes had ruptured 24 hours prior to delivery, all babies of precipitate deliveries, and all babies with the respiratory distress syndrome. Since there was no effort to control the obstetrical practices for this group of patients, the use of analgesic and anesthetic agents reflects the usual management employed by the full-time obstetrical staff. Meperidine and Phenergan were given to 13 mothers, no analgesic agents to 11 mothers, meperidine and atropine to 7 mothers, meperidine

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alone to 7 mothers and meperidine and Nembutal to 6 mothers. The total dose of meperidine rarely exceeded 100 mg N_2O-oxygen anesthesia was given to 19 mothers, N_2O-oxygen with pudendal block to 13 mothers pudendal block alone to 11 mothers, no anesthesia to 5 mothers. Other analgesic agents, including scopolamine were given in combinations which are not mentioned because of their infrequency Other anesthetic agents, including cyclopropane and Trilene and saddle block anesthesia were used for a few deliveries.

The temperature of the delivery room was maintained at 5 to 80°F The umbilical cords of the infants were clamped and tied immediately The air passages were cleared by a bulb syringe At 1 minute of life an Apgar rating* was performed by the attending pediatrician. Following this a complete physical examination was performed Approximately one-half hour after birth the infant was wrapped in a cotton blanket and removed to the air-conditioned newborn nursery approximately 150 feet away A rectal temperature was taken and the baby was kept loosely wrapped warmed slightly by a 60-watt incandescent lamp

In the nursery electrocardiograms and phonocardiograms were made on two or three occasions in each newborn infant and were performed with the babies supine The electrocardiogram was taken first, and the phonocardiogram immediately afterward The initial pair of records was obtained within the first hour of life in 26 infants, and within the first 2 hours in an additional 27 infants. In 6 others the initial records were made within the first 3 hours, and the time was 4 and 6 hours, respectively in another 2 infants.

The second records were obtained between 22 and 44 hours after birth and the third when possible between 44 and 165 hours. A Sanborn Twin Beam Cardiette was used with paper speed set at 25 mm. per second Small electrodes (2 by 5 cm) were used on the extremities A special rubber belt was used to locate the precordial lead positions in a uniform manner Holes had been placed in this belt in appropriate locations for the 6 conventional chest leads (V_1-V_6) as well as 2 right-sided leads (V_{3R} and V_{4R}) Inserted into the holes were 8 copper studs intended to recei e snugly the tip of the chest lead wire. The use of the rubber belt facilitated the taking of precordial leads with minimal artifact resulting from movement of the patient The accuracy of replacement of the precordial electrodes was also enhanced by this method

Electrocardiograms were analyzed for rate, rhythm P R interval morphology of the P wave Q-T interval corrected for heart rate (Q-T) and axis. The axes were determined by the method of Hurst and Woodson [11] The directions of *QRS* and T vectors in the frontal plane and horizontal plane were determined and plotted for each of the three time periods mentioned above.

The inaccuracies of the methods particularly with respect to the plotting of the vectors in the horizontal plane, are recognized [12] and therefore points were placed merely within 30-degree segments. Nevertheless, this method permitted an appraisal of the gross changes that occurred in the T wave vector in the first few days of life, as described under results, below

The phonocardiograms of the subjects of Group A were recorded by a 2.4-cm. bell stethoscopic end piece at 75 mm. per second with "logarithmic" amplification Records were made at the apex, lower left sternal border pulmonic region and aortic area.

Group B Studied by tape-recorded heart sounds. Nineteen additional newborn infants, selected in a manner similar to that described under Group A were studied earlier after delivery by more intensive phonocardiographic methods utilizing a tape recorder Records were made at the apex, lower left sternal border and pulmonic area.

The observations were made as soon after birth as possible the earliest initial observation being at 10 minutes of age and were repeated every 10 to 15 minutes during the first 2 hours of life every half hour for the following 2 hours and every hour thereafter up to 8 hours of age. A total of 237 examinations was made on the 19 infants.

*The Apgar rating evaluates the heart rate, respiratory effort, muscle tone, color and response to tactile stimulation of the newborn infant. A score of 10 indicates that an infant is in the best possible condition, lower scores indicate asphyxia.

A bell stethoscopic end piece 2.4 cm in diameter was attached to the microphone.* Recordings were taken on an Ampex tape recorder Model No 401 A The tapes were then analyzed by a system of 4 Krohn Hite band pass filters. A description of the analysis system follows Band I passed 90 per cent of sounds between 200 and 600 c.p.s. Band II passed 90 per cent of sounds between 100 and 400 c.p.c Band III passed 90 per cent of sounds between 30 and 130 c.p.s. Band IV passed 90 per cent of sounds between 30 and 800 c.p.s Band III gain is twice the gain of Band II Band II gain is twice the gain of Band I The four simultaneous curves were displayed on an oscilloscope and reproduced on photographic paper using a Hathaway 4-channel recorder Since this method does not include a simultaneous electrocardiogram the timing of phonocardiographic phenomena such as murmurs and ejection sounds was related to the onset of the rapid vibrations of the heart sounds. The presence of constant background vibration made the very low frequency band (Band IV) unsuitable for analysis and interfered somewhat with Band III Details suitable for study were consistently available in the two bands of higher frequency as described

Results

Group A

1 ELECTROCARDIOGRAMS.

a. Rate The mean rates were 129±12.5† 128±12.5 and 135±13.8 per minute for the three time periods respectively

b Rhythm The rhythm was of sinus origin in all instances and no arrhythmias were noted

c. P R interval The mean P R intervals were 0.123 0.112 and 0.112 second for the three time periods respectively

d P waves In the second and third time periods the P waves tended to become taller and more peaked than in the first

e. Q-T The mean Q-T intervals were 0.422±0.037 0.412±.027 and 0.401±0.031 second respectively for the three time periods. The decrease was considered not to be significant

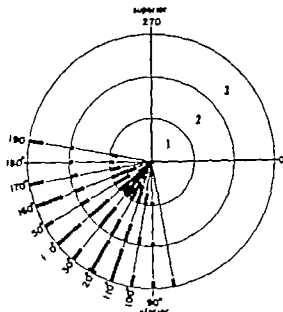


Fig 1 ÂQRS in the frontal plane. The inner circle represents the first time period 0 to 6 hours after birth the band marked 2 represents the second time period 22 to 44 hours and the outer band 3 represents the third time period 44 to 165 hours.

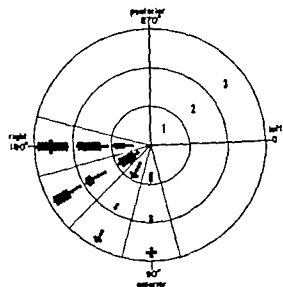


Fig. 2 ÂQRS in the horizontal plane Time periods as in Fig 1

f (1) ÂQRS in the frontal plane (Fig 1) —The mean was 137±21.4 degrees for the first time period In the second time period the mean was 134±24.4 degrees, and in the third time period the mean was 133±26.8 degrees. The change in axis in the frontal plane was considered not to be significant (2) ÂQRS in the horizontal plane (Fig 2)—

*Altec Condenser Microphone M 11 System, ... frequency range of 20 to 18,000 c.p.s.

†Standard deviation.

The means were 157±25.8 164±24.3 and 158±28.3 degrees. In this plane also the change of QRS axis was insignificant. (3) ÂT *in the frontal plane* (Fig 3)—*The* mean in the first time period was 57±48 5 degrees in the second time period it was 38±35 4 degrees, and in the third time period 26±31 degrees. There was then a trend of the T wave vector in the frontal plane toward 0 degree The data were very widely grouped in the first time period but in the later time periods there was less variation. (4) ÂT in the horizontal plane (Fig 4)—The mean axis in the first time period was 64±63 4 degrees. In the second time period the mean was −33±53 9 degrees, and in the third time period it was −68±27.3 degrees. The trend from an anteriorly placed vector to a sharply posteriorly directed one is very striking between the first and second time periods. The scatter of the data diminishes between the first and third time periods.

2. PHONOCARDIOGRAMS.

a The rate and the rh thm showed no significant differences from that found in the electrocardiograms.

b The first sound was best recorded at the apex and lower left sternal border The time of onset of the main rapid vibra tions from the onset of the Q wa e was 0.041 second average with a range of 0 03 to 0 05 second The first sound often appeared to be split to the extent of 0 02 second with splitting being best observed at the lower left sternal border

c The second sound was best recorded in the pulmonic area. Because of the fre quency response of our apparatus we did not attempt to detect splitting of 0 01 second or less, and sounds that were split less than 0 02 second were defined as single n Group A studies. In the initial time period the second sound was single" in 51 of 61 observations, whereas in the second time period it was single in 22 of 44 observations. In the th rd time period the second sound was single in only 20 of 57 observations. When spl tting oc curred maximum separation was 0 03 second between the two components but was rarely this wide. Splitting of 0.02 second was noted in 90 per cent of the nstances in which separation of the two components was present

d Ejection sounds or systolic clicks (Fig 5) were present in 93 per cent of the newborn infants in the first time period but the frequency diminished to 88 per cent in the second and to 67 per cent in the third periods respectively There was, in addition a lessened intensity of the sound in the third time period in 8 cases.

e. Of the 61 infants 22 showed murmurs of the types to be described. None of these patients revealed continuous murmurs.

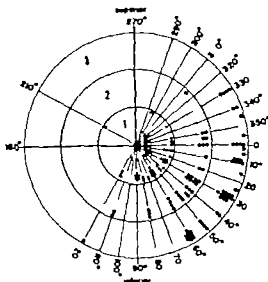


Fig 3 ÂT in the frontal plane. Time periods as in Fig 1

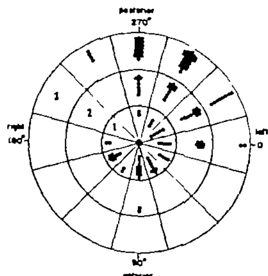


Fig. 4 ÂT in the horizontal plane. Time periods as in Fig 1

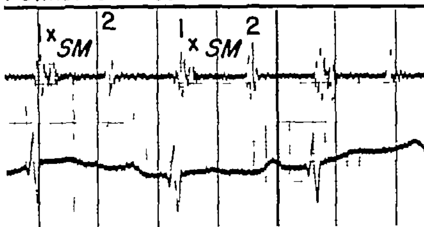


Fig. 5. Ejection sound or systolic click (*X*) followed by a low-intensity systolic murmur.

The incidence of murmurs was highest in the first time period (28 per cent) and diminished in the second and third time periods. (1) Decrescendo murmur of low intensity and low frequency maximal in the pulmonic area, occupying the first half to two thirds of systole (Fig. 6). This most common murmur was noted in 16 newborn infants, most often in the first time period. (2) A crescendo-decrescendo murmur of varying frequency and intensity maximal at left sternal border with peak intensity from early to mid systole. This was observed in 6 newborn infants, again with diminishing incidence in the three time periods. (3) A crescendo murmur in late systole, of high frequency and low to moderate intensity (Fig. 7). This was observed in only 2 instances and in the first time period exclusively. In one case it was maximal in all four areas studied and in the other along the left sternal border and pulmonic area.

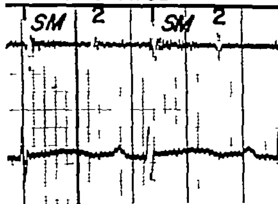


Fig. 6. Decrescendo systolic murmur occupying the first two thirds of systole.

Group B. With the more precise recording of the heart sounds by the technique described for this group, time intervals were measured in milliseconds.

1. FIRST HEART SOUND. The first heart sound was found to be split at the time of the initial recording in all 19 infants, and the degree of splitting remained unchanged for the first 8 hours. The average interval between the first and second component was 19.7 msec. with the range being 17.0 to 23.0 msec.

2. EJECTION CLICKS. Two ejection clicks were observed: the first an average of 39.7 msec. after the first component of the first sound, ranging from 32 to 50 msec., and the second click an average of 63.9 msec. after the first component with a range of 51 to 70 msec. (Fig. 8). The initial click was recorded in all 19 infants and in 88.7 per cent of the examinations. The second click was recorded in 15 of the 19 infants and in 48.8 per cent of the examinations.

3. SECOND HEART SOUND. The interval between the two components of the second sound consistently widened as time passed. An initial split of approximately 10.8 msec.

widened to an average of 19.4 msec. 6 to 8 hours after birth (Fig. 9)

4. THIRD HEART SOUNDS. Third heart sounds were observed in 2 infants.

5. MURMURS. Two murmurs with onset in mid-systole increased in intensity up to *but not beyond the second sound*. These murmurs were short lived.

In summary, during the first 72 hours these normal newborn infants exhibited (1) tendency for peaking of the P wave to appear, (2) anteriorly directed ÂT which rapidly moved around to a posterior direction, (3) rightward ÂQRS which remained constant, (4) an early systolic click *in the phonocardiogram* appearing almost universally at birth but with diminishing frequency later, (5) a second systolic click in some subjects, (6) narrowly split second sound at birth with tendency to split more widely later, (7) infrequent appearance of transient low intensity murmurs, and (8) no significant differences of electrocardiograms or phonocardiograms relative to sex or race.

Discussion

Obstetrical factors. The striking difference *in the incidence of heart murmurs in these* normal newborn infants as compared to incidence *in the babies* studied by Burnard and Braudo[4] may result from our selection of subjects who were the products of uncomplicated deliveries. These infants were delivered after limited use of analgesic and anesthetic agents in a manner practiced in many institutions in the United States.

In the studies, no correlations were found between obstetrical factors and any of the following: persistence of murmurs, failure of pulmonic second sound to separate, failure of T vector to revolve posteriorly in the horizontal plane, or unusual clicks. However, 5 of 10 newborn infants (50 per cent) who received oxygen by mask because of breathing difficulty were observed to have heart murmurs. Of these 10 subjects who required resuscitation with oxygen, no significant differences from the the other 51 infants were observed in relation to presence of clicks, splitting of P_2, or T wave evolution. Neither of the 2 babies in Group A with systolic crescendo murmurs up to the second heart sound, *presumably originating from the ductus arteriosus*, had required resuscitation. Other obstetrical factors, including the Apgar rating at 1 minute, the baby's temperature upon arrival at the nursery, use of particular analgesic and anesthetic agents, maternal age and parity, showed no particular influences on the electrocardiographic and phonocardiographic parameters.

Thus, with obstetrical practices such as those described, using limited analgesia and anesthesia and mild resuscitative measures, characteristic electrocardiographic and phonocardiographic patterns are observed in the newborn infant. He usually does not have a murmur from the ductus arteriosus.

Electrocardiograms. The increase in P wave amplitude in the second and third

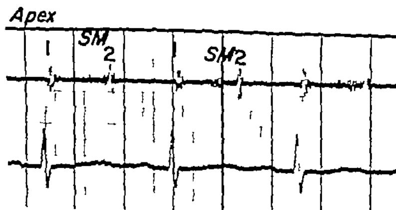
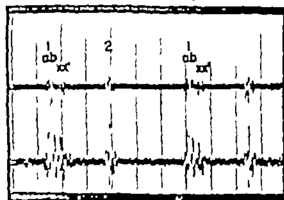


Fig. 7. Crescendo murmur in late systole. This particular murmur was seen in all four areas.



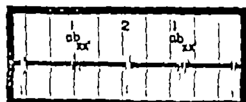


Fig. 8. Examples of tw of the Group B subjects showing tracings filtered through Bands I and II as described in the text. Not first nd second jec tion licks (X nd (Y

time periods may be relatable to closure of the foramen ovale as the right atrium assumes the role of collecting all the blood from the inferior vena cava as well as that from the superior vena ca a. This finding was also noted by Ziegler

The mean QRS axis in the frontal plane during the first time period was similar to that described n newborn infants of 0 to 24 hours of age by Ziegler who found an average ÂQRS of 137 degrees, with a range from 75 to 190 degrees. The spatial orientation of the ÂQRS is consistent with the relative hypertrophy of the right ventricle present at birth

In contrast to the stability of the ÂQRS there was a marked shift in the T wave vector during the three periods of observation. In the horizontal plane at birth the ÂT was found to be directed anteriorly manifest by positive T waves in right-sided Leads V_{3R} and V_{4R} as well as in Leads V_1 and V_2. The striking movement of ÂT posteriorly during the second and third time periods is shown by a change to negativity in the T waves of the right sided precordial leads. This posterior swing of the ÂT has been noted previously[18] and has been attributed to a lessening of the right ventricular hypertension that is normally present at birth.[19,21] In some situations in which this physiologic adjustment fails to take place because of congenital heart disease persistence of the positive T waves in right-sided precordial leads is interpreted as evidence of right ventricular hypertrophy in young infants.[1]

Interesting modifications in the evolution of the electrocardiogram in infancy have also been noted by Peñaloza and associates[13] in normal babies born at high altitudes (14 900 feet). Here the T waves in right-sided precordial leads were noted to be upright at birth just as in control subjects at sea level. A few hours to 3 days after birth a change occurred with negativity of the T waves becoming apparent in right-sided precordial leads, both at sea level and at high altitudes. A few weeks later however T wave positivity in right-sided precordial leads was again noted, accompanied by an accentuated right ÂQRS deflection and a tall R in Lead V_1. These changes were in striking contrast to the evolution observed at sea level. The persistence of right ventricular preponderance thus manifested electrocardiographically was attributed to the continued presence of a fetal structure of the pulmonary arteries and arterioles frequently noted in the lungs of children at high altitude thus, in turn leading to continued pulmonary hypertension

Phonocardiograms. The two time intervals from the Q wave to the onset of the first component (41 msec.) and from the Q wave to the onset of the second component (61 msec.) of the first heart sound may correspond with Heintzen's time intervals of QIa and QIb respectively.[8] Although he did not analyze the first sounds of infants less than 2 years of age Heintzen's QIa time in the 2 to 3-year-old group was 48.1 ± 0.55 msec. and the QIb time in this same age group was 66.8 ± 1.12 msec. both shorter than the intervals of older children. He presented evidence that strongly indicated that the first com

ponent of the first sound (Ia) originated from closure of the mitral valve, and that the second component (Ib) originated from closure of the tricuspid valve. Braudo found that these two components of the first sound were of equal intensity in the pulmonic area but that the second component was louder in the tricuspid area of his newborn infants thus also indicating that the second component originates from closure of the tricuspid valve. However Braudo's QIa time averaged 45 msec. and the QIb averaged 70 msec.

Our studies using the methods outlined for Group A revealed early clicks in 93 per cent of the newborn infants during the early hours of life. Using improved recording techniques in the Group B studies we were able to demonstrate these clicks in all newborn infants studied during th first hours. In addition a second click was observed in a majority of newborn infants. The first click appeared 39 7 msec and the second 63 9 msec. after the onset of the first sound The origins of these clicks remain obscure. Perhaps they result from tensing of the great vessels the aorta being subject to higher pressures than before birth and the pulmonary artery maintaining a high pressure during the early hours.

An alternate explanation is that the first ejection click originates with distention of the pulmonary artery and the second with th arrival of the aortic pulse wave at the ductus.[1]

Splitting of the second sound was minimal at birth and could not be measured under the conditions described for the Group A subjects However an attempt was made to delineate splitting of as little as 0 01 second using the techniques described for the Group B subjects. It was apparent that the closure of the aortic and pulmonic valves was nearly simultaneous soon after birth but that consistent slight splitting was apparent within several hours. This split was usually approximately 0.02 second and never greater than 0 03 second. It was observed in approximately two thirds of the subjects with standard phonocardiographic methods by the third time period (45 hours after birth) but was observed more consistently in the Group B studies, as shown by Fig 8. Even splits of 0 02 second are difficult to detect by clinical auscultation and yet this finding is often very critical in the diagnosis of congenital malformations of the heart in the neonate.

The incidence of heart murmurs in this study differs strikingly from that in previous investigations. Three of the four types of murmurs described by Braudo were detected but the fourth type—the continuous murmur—was not encountered in the 80 subjects studied

The most common murmur a decrescendo murmur of low intensity and low frequency has characteristics similar to those of functional murmurs heard later in childhood [4] This murmur began after the fragmented first sound and stopped appreciably before the second sound It was heard well at the pulmonic area and usually along the left sternal border It was detected less frequently in the last time period than initially

From the foregoing discussion it is apparent that the electrocardiogram and phonocardiogram reflect some of the hemodynamic changes that occur during the neonatal period Adams[14] and Eldridge and Hultgren have shown that in the human infant the ductus does not close completely at birth but often remains slightly patent permitting flow from the

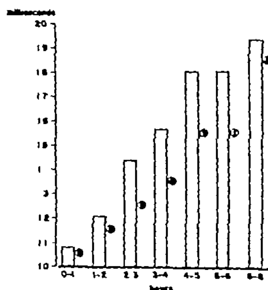


Fig 8 Splitting of the second sound in milliseconds and time. The number of observations are indicated by the encircled figures.

vessel of higher pressure. Dawes[24] found that the closure is a result of increased arterial oxygen tension acting directly on the ductus muscle and that the presence or absence of a murmur in the newborn lamb is related to the turbulence produced by the flow of blood through the ductus. When the flow through the ductus is very great, there may be no murmur, and likewise, when the flow is very small, no murmur may be audible. In the unanesthetized lamb delivered by Caesarean section the systemic and pulmonary arterial pressures remain nearly identical, often for as long as one half hour. When the lamb is given 100 per cent oxygen to breathe, the systemic systolic pressure rises, whereas the pulmonary arterial pressure remains quite constant.[21] Presumably, as the tension of arterial oxygen increases in the newborn infant, closure of the ductus arteriosus is facilitated, but at the same time the systemic arterial pressure is raised above the pulmonary arterial pressure.

In the fetal circulation, the ventricles work essentially in parallel against a single peripheral resistance. Thus, throughout gestation the right ventricle performs work quantitatively similar to that done by the left ventricle, and this is reflected in an electrocardiogram at birth that has certain features of right ventricular preponderance. Soon after birth the two circulations begin to work *in series*. Dawes has estimated a twelvefold increase in pulmonary blood flow, whereas systemic flow remains about the same in the newborn lamb. This increase in blood flow is brought about primarily by the decrease in pulmonary resistance as a result of ventilation of the lungs. If the ductus remains open, the pulmonary blood flow will be even greater than the systemic flow as a result of left-to-right shunting. The increase in flow through the right circulation produced by these changes might be expected to produce more dilatation of the right atrium, reflected in increased amplitude of the P waves on the electrocardiogram, and to produce a longer right ventricular systole with delayed closure of the pulmonic valve manifested by increasing splitting of the second heart sound on the phonocardiogram. The pulmonary artery is dilated by the increased pulmonary blood flow, and the aortic pressure is raised, factors which would be expected to produce ejection clicks. Finally, as the pulmonary arteriolar resistance falls and the pulmonary blood flow falls with ductal closure, the right ventricular work load diminishes, as evidenced by the striking shift in the T wave vector in the horizontal plane.

Summary

1. Simultaneous phonocardiograms and electrocardiograms were taken serially in 61 newborn infants, in order to study the relationship of the auscultatory findings to the electrocardiographic alterations known to occur during the first few days of life.

2. A second group of 19 infants was studied more intensively by phonocardiography, using tape recording methods, during the first 8 hours of life.

3. Electrocardiograms during the first 72 hours of life showed: (a) tendency for peaking of the P waves to appear, (b) anteriorly directed ÂT which rapidly rotated to a posterior position, and (c) rightward ÂQRS which remained constant.

4. Phonocardiograms in data derived from both groups showed: (a) an early systolic click appearing almost universally at birth but with diminishing frequency later—its timing averaged 39.7 msec. after the onset of the first sound, (b) a second systolic click in some subjects, averaging 63.9 msec. after the onset of the first sound, (c) narrowly split second sound at birth with a tendency to a wider split later (average 19.4 msec. at 6 to 8 hours of life), (d) transient low intensity systolic murmurs noted in approximately one third of the infants. These were of three varieties: the most common type was a decrescendo murmur in the pulmonic area, less commonly seen were crescendo-decrescendo murmurs, and rarely (4 instances) the timing was in late systole. No diastolic murmur was seen.

5. The probable relationship of the electrocardiographic and phonocardiographic findings to the alterations in circulation that occur at birth are discussed.

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A correlative study between the radiologic and pathologic diagnoses of atherosclerosis of the aorta

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Among the methods available for the epidemiological study of atherosclerosis, radiologic investigation could play an important part. A recent study group concluded that roentgenography of the heart has no place at present in field surveys of coronary heart disease. The same group believed that the roentgen method may be of some value in the diagnosis of aortic atherosclerosis but further study was recommended with the purpose of evaluating the method.

In this article, we report a roentgen and postmortem correlative study carried out in an attempt to evaluate the reliability of the various x-ray signs of atherosclerosis of the thoracic aorta and to determine the usefulness of this method in field surveys.

The aorta is easily visible in chest films and the latter do not require special preparation of the patient, as is the case with radiologic study of the abdominal aorta. Even after cleansing enemas, gas and feces are liable to remain in the intestine, especially in elderly people, and to obscure calcifications of the aortic wall. Moreover, the wall of the abdominal aorta is not visualized on x-ray film, so that the presence of calcification is the only roentgenologic sign of atherosclerosis. Therefore, chest films might be more suitable in field surveys aimed at detecting radiologically the presence and degree of atherosclerosis of the aorta.

Material and methods

In a consecutive series of 842 autopsies on men and women over the age of 30, 190 cases were found in which a routine standard chest roentgenogram (postero-anterior, upright, at a distance of 6 feet) had been taken within the 6 months prior to the death of the patient.

The present study is based on these 190 cases; the age and sex distributions of the subjects are shown in Table I. The chest x-ray films had been taken for various diagnostic purposes without prior knowledge that they would be used later in this survey, so that standard optimal exposures for the detection of aortic calcification were not used. The films were read by the radiologist (A.S.) without knowledge of the patient's age or disease or the autopsy findings.

All the films were read twice at an interval of 2 weeks. A third reading was made in the relatively few cases in which there was a difference between the first two appraisals. This reading was then compared with the two previous ones, and in all cases was found to be identical with

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one of them. The two identical readings were accepted as the final diagnosis.

The radiologic assessment of the degree of atherosclerosis was based upon the presence and extent of elongation calcification and dilatation of the thoracic aorta. Each of these signs was graded separately as zero one-plus and two-plus. Finally the over-all degree of atherosclerosis was graded as severe or "moderate, or a notation of no atherosclerosis was made.

Severe atherosclerosis was diagnosed when a marked (++) elongation and dilatation was associated with considerable (++) deposits of calcium in the thoracic aorta in sites other than the site of insertion of the ligamentum arteriosum.

Moderate atherosclerosis was diagnosed in cases which showed moderate (+) elongation and dilatation with or without calcification or in cases which showed marked (++) elongation and moderate (+) or no calcification.

Dilatation alone is considered to be an unreliable radiologic and pathologic sign of atherosclerosis because it is often present in aged or hypertensive subjects with or without aortic valvular lesions in the absence of atherosclerosis.[6] The mere presence of dilatation was therefore not regarded as an indication of atherosclerosis in our study

The *pathologic examination* consisted in recording the extent and the type of the atherosclerotic lesions in the entire formalin-fixed aorta as reported in an earlier article.[7] On the basis of the extent and type of the lesions an atherosclerotic index of the aorta was determined

As was found in a pathologic study of the whole series of 842 autopsies an index of up to 1.0 can be considered for practical purposes, to signify the absence of atherosclerosis. Aortas with an index which ranged between 1 1 and 10 showed atheromas and/or fibrous plaques but either no or minimal complicated lesions and were classified therefore, as showing moderate atherosclerosis. Aortas with an index above 10 1 and ranging up to 50 usually showed many complicated lesions (ulcerations, mural thrombi or marked calcification) and were considered as showing "severe" atherosclerosis.

Table I. Age and sex distribution in the 190 cases on which the correlative study was made

Age range (yr.)	Males	Females	Totals
30–39	7	8	15
40–49	12	18	30
50–59	30	22	52
60–69	32	12	44
70–79	33	11	44
80–89	3	2	5
Totals	117	73	190

A careful search was made for areas of calcification and their site and extent were recorded on drawings of the aortic outline. Calcification at the site of insertion of the ligamentum arteriosum was not considered in this study

The circumference of the aorta was measured at two different levels 1 cm above the ostia of the coronary arteries and at the level of origin of the fifth intercostal arteries. These values were compared with the radiologic estimation of dilatation and of atherosclerosis.

Results

The results of the comparison between the radiologic diagnosis of atherosclerosis of the thoracic aorta and the pathologic findings as expressed by the atherosclerotic index of the entire aorta are shown in Fig 1 The accuracy of the radiologic diagnosis varied between the different pathologic groups.

In the group with no pathological changes (index 0-1) the radiologic diagnosis was correct in 28 of 43 cases (65 1 per cent)

In 85 cases of anatomically moderate atherosclerosis (index 1 1 10) the radiologist was able to make an accurate diagnosis in 53 cases (62.3 per cent) In 10 cases (11 8 per cent) an overdiagnosis of the degree of atherosclerosis was made and in 22 cases (25 9 per cent) an underdiagnosis was made

In the 62 cases which showed "severe" pathologic lesions (index 10 1 50) the radiologic diagnosis was accurate in 25 cases (40.3 per cent) but the presence of "moderate" atherosclerosis was noted radiologically in an additional 34 cases (54.9 per cent) In only 3 cases did the athero-

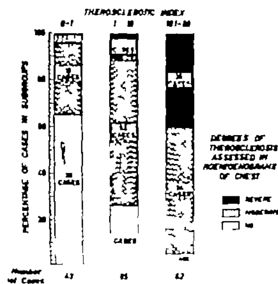


Fig. 1 Comparison between roentgenologic and anatomic diagnosis of atherosclerosis of aorta.

sclerosis remain undetected on radiologic examination.

The results show therefore that the radiologist was able to detect the *presence* of atherosclerosis in at least 74 per cent of the cases but the assessment of the *degree* of atherosclerosis was less accurate.

Comparison of the individual radiologic signs involved in the diagnosis of atherosclerosis with the corresponding pathologic findings, as well as with the anatomic degree of atherosclerosis showed the following results.

Calcification. Calcification observed in x ray films was too often referred to the aorta. Thus, the presence of aortic calcification was confirmed in the pathologic specimen in only 29 of 75 cases with radiologically demonstrable calcification. Because of this lack of correlation between radiologically and anatomically observed calcification there is little value in comparing radiologic calcification and the anatomic degree of aortic atherosclerosis. However absence of radiologic calcification was practically always confirmed in the pathologic specimen (102 of 115 cases).

Elongation. No comparison was attempted between radiologic elongation and its anatomic counterpart.

The radiologic degree of aortic elongation and the anatomic degree of atherosclerosis are compared in Table II. Only 8 of 43 cases (18.6 per cent) with no atherosclerosis showed radiologic elongation. On the other hand 63 of 85 cases (74 per cent) with moderate atherosclerosis and 57 of 62 cases (92 per cent) with severe atherosclerosis showed elongation on the chest films.

Dilatation. The radiologic grading of dilatation showed a poor correlation with the circumference of the fixed aorta and with the degree of atherosclerosis.

Discussion

The most important generally accepted radiologic signs of aortic atherosclerosis are calcification and elongation.[1-4,8,16] In our material we considered calcification of the aorta as a relevant sign only when it appeared in a location other than the insertion of the *ligamentum arteriosum.* Calcification located in the aortic arch is not an unequivocal sign of atherosclerosis, since it may appear in the scar of the insertion of the ligamentum arteriosum and at the origin of the great vessels and be unrelated to the presence or severity of aortic atherosclerosis.[17,18] Moreover calcification in the arch may be due to syphilitic aortitis without generalized atherosclerosis of the aorta.[8,11,12,19,20]

The radiologist was always able to detect those cases in which marked calcification was seen by the pathologist. There were, however numerous cases in which the radiologist reported calcification but none was found on pathologic examination. This can be explained by the fact

Table II. Comparison between the radiologic degree of aortic elongation and the anatomic degree of atherosclerosis

X-ray degree of elongation	Atherosclerotic index		
	0-1.0	1.1-10.0	10.1-30.0
N (−)	35	22	5
Moderate (+)	7	53	31
Severe (++)	1	10	26
Number of cases	43	85	62

that only posteroanterior roentgenograms were used and calcifications which projected into the aortic shadow from extra aortic sites (lung lymph nodes, calcified costal cartilages calcification in the bronchial wall) were misdiagnosed as aortic calcification An additional lateral film of the chest might have eliminated this source of error to a certain extent and contributed to a higher accuracy of radiologic estimation of calcification.

The cases with anatomically proved calcification were equally distributed between the moderate (index 1 1 10) and the severe (index 10 1 50) atherosclerotic groups. We were thus unable to confirm the observation of Hyman and Epstein[14] that 80 per cent of the cases with anatomic calcification belong to the group with advanced atherosclerotic lesions.

It is also apparent from our results that calcification in the thoracic aorta even when marked should be accepted as an indication of severe atherosclerosis only in the presence of marked elongation.

The significant correlation between the presence of radiologic elongation of the aorta and moderate or severe atherosclerosis suggests that elongation is the most constant single radiologic sign of atherosclerosis.

Dilatation of the thoracic aorta seen on the x-ray films corresponded with the measurements in the fixed specimens in only 52 per cent of the cases. This poor correlation can be explained by the difference between the size of the aorta in vivo and that after fixation in formalin which produces shrinkage of varying degree.

As shown in Fig 1 the accuracy of the radiologic diagnosis as to the presence of atherosclerosis was 95 per cent in the severe and 74 per cent in the moderate group. These results indicate that the radiologist is able to detect the *presence* of aortic atherosclerosis in a high proportion of cases according to the combined criteria used in our study On the other hand, the *degree* of atherosclerosis can be less readily assessed.

The inaccurately diagnosed cases can be divided into radiologically under diagnosed and overdiagnosed groups.

The underdiagnosis" can be explained by the well known fact that the thoracic aorta may be only slightly involved even in severe atherosclerosis because the abdominal aorta is usually the site of the most severe changes. Since the atherosclerotic index in this study was based upon the entire aorta the discrepancy is not surprising An additional explanation for the underdiagnosis can be found in the roentgenologic technique. On films obtained with longer exposures the calcifications may become blurred and invisible. This would explain the failure to detect in the chest films calcifications which were found on pathologic examination

In order to evaluate the causes of over diagnosis the 25 cases in this category were analyzed as to the underlying disease. It was found that 6 patients had either scoliosis or mediastinal inflammatory disease which had caused radiologic distortion of the aorta. Five patients had chronic renal disease associated with hypertension hypertrophy of the left ventricle and dilatation of the aorta. In 5 additional patients, all of whom were over the age of 65 years, marked dilatation of the aorta was found both radiologically and pathologically In these 10 patients the dilatation of the aorta may have been the upgrading factor in the radiologic interpretation This is additional confirmation that dilatation of the aorta has little relation to the degree of atherosclerosis[8] and is, therefore, unreliable in the roentgenologic estimation of atherosclerosis.[4-8] In 5 patients the projection of calcification of extra aortic origin upon the aortic shadow was the probable cause of the radiologic over diagnosis. In the other 4 patients the radiologic overdiagnosis of the degree of atherosclerosis remained unexplained

It is clear to us that the atherosclerotic index chosen to designate the degrees of aortic atherosclerosis has shortcomings when used for a comparison with a clinical method The advantage of the index lies mainly in its simultaneous expression of the extent and severity of the lesions. Its main disadvantage is in the use of a mathematical expression for the quantitation of a biologic process and the arbitary choice of certain index ranges to delineate the varying degrees of atherosclerotic severity

In conclusion it may be stated that from a single posteroanterior chest radiogram the radiologist is able to detect the presence of aortic atherosclerosis in a high proportion of cases. The results could be improved in a planned survey by ensuring that chest films of high quality are obtained and by taking into account the age and blood pressure of the patient when assessment of the radiologic findings is made. The radiologic estimation of atherosclerosis should be based on the degree of elongation of the aorta and on the presence, location, and extent of calcification.

To exclude errors in the location of calcification a lateral chest film would be very helpful. The sole finding of dilatation of the thoracic aorta should be regarded as an unreliable sign of atherosclerosis, since it is largely dependent on aging and may be *influenced by the presence of aortic* valvular disease and/or hypertension.

Summary

1. The pathologic and radiologic findings of atherosclerosis of the aorta have been compared in 190 subjects who were over the age of 30 years.

2. The reliability of the radiologic signs of atherosclerosis has been discussed and attention drawn to the positive diagnostic value of elongation and calcification and the unreliability of dilatation of the thoracic aorta. The presence of calcification alone does not indicate the presence of severe aortic atherosclerosis.

3. Routine posteroanterior chest films constitute a useful and easily applicable procedure in the detection of aortic atherosclerosis.

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Experimental and laboratory reports

Myocardial bridges in coronary angiography

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Myocardial bridging of the coronary arteries was first described by Geiringer[1] in 1951 Since that time Edwards, Burnardes, Swarm and Lansing have described the appearance of the over bridgings in 5 4 per cent of 276 hearts examined Polacek[7] reports their incidence of occurrence to be 85 7 per cent in 70 hearts examined In 1960 Porstmann and Iwig[4] reported this intramural stretch of the coronary artery to be visualized in a coronary angiogram taken on a human patient, although anatomic verification was lacking The present study concerns the angiographic visualization of such myocardial bridgings in canine hearts in which there have been follow up post mortem examinations.

Techniques Coronary angiograms were obtained in 23 normal mongrel dogs. Approximately 95 injections of contrast media were performed in the 23 animals. A specially constructed catheter[4] was maneuvered into the supravalvular segment of the aortic arch either via the carotid or the femoral arteries. Twenty cubic centimeters of 90 70 or 50 per cent Hypaque was injected by means of the Gidlund automatic injector[4] at a pressure of 5 to 6 kilograms per square centimeter or by means of a manual injector Injection of the contrast media was made either after asystole produced by acetylcholine or during the regular rhythm of the cardiac cycle

Schonander angiograms were recorded at the rate of 3 films per second for a period of 5 to 7 seconds. During the injection Lead II of the electrocardiogram was recorded on the Sanborn ECG recorder for purposes of monitoring the injection. The duration of the injection was automatically recorded on the Sanborn ECG recorder

After completion of the experimental studies the animals were sacrificed and the



Fig 1 Dog No. 20. Coronary arteriography is performed during acetylcholine arrest of normal canine heart. The angiogram pictured was taken 0 7 sec after the injection of 90 per cent Hypaque. The left anterior descending coronary artery (arrow) is filled evenly throughout its course and assumes the usual oxbow curve N myocardial bridges were seen in this heart at postmortem examination.

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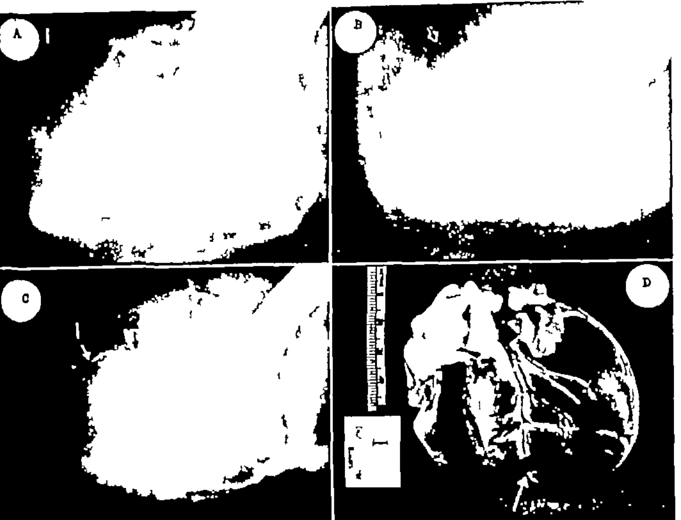


Fig. 2. Dog No. 12. *A*, Coronary arteriography during the regular cardiac cycle. The film I taken 2.7 sec. after the I jection of 90 per cent Hypaque. Reflux of dye into the left ventricle has occurred and outlines the chamber. A sharply angular V-curve (*1*) is seen in the left anterior descending coronary artery distal to the origin of the pical branch (*2*). *B*, Film taken 4.0 sec. after the injection of 90 per cent Hypaque *during the regular cardiac cycle demonstrates* gradually sloped V bend (*arrow*) t the same site described in *A*. *C*, Coronary ngiogr phy during acetylcholine rrest of the heart. A gradually sloped V-curve distortion (*1*) in the left nterior descending coronary artery shadow persist on all films. This is located distal to the origin of the pical branch (*2*). *D*, Gross photograph of the heart shows band of myocardial fibers (*1*), 7 mm. in width, crossing over the left anterior descending coronary artery t site 1 cm. distal from the origin of the apical branch (*2*).



Fig. 3. Dog No. 12. *A* and *B*, Coronary arteriography is performed during the regular cardiac cycle. Film *A*, taken 3.3 sec. after the injection of 90 per cent Hypaque shows complete filling of the left anterior descending coronary artery. In film *B*, taken 4.3 sec. after the injection of 90 per cent Hypaque, a shallow depression (*1*) is transiently localized in the left anterior descending coronary artery, shallow at the site of emergence of the septal branch (*2*). *C*, Coronary angiography performed during acetylcholine arrest of the heart demonstrates uniform filling of the left anterior descending coronary artery throughout its course. *D*, Cross photograph of the heart shows a small band of myocardial fibers (*1*), 4 mm. in width, crossing over the left anterior descending coronary artery just proximal to the site of origin of the septal branch.

hearts were examined grossly. If myocardial bridgings were present, their locations were marked and gross photographs were taken.

Myocardial bridges were defined in accordance with Polacek's report.[7] Bridges are present when the coronary artery dips under the superficial layer of ventricular myocardium and, after a course of variable length, reappears on the surface of the myocardium.

Observations

Gross postmortem examination of the 23 dogs revealed myocardial bridges to be present in the hearts of 2 animals. In both instances, angiograms had been obtained with and without the use of acetylcholine. In Dog No. 12, coronary angiography performed during the regular cardiac cycle (Fig. 2,*A* and *B*) showed marked distortion of the usual oxbow curve of the left anterior descending coronary artery approximately 6 mm. beyond the site of origin of the apical branch. This distortion ranged from a gradually sloped V-bend to a sharply angular V-curve, suggestive of a local constriction in successive films. During arrest with acetylcholine (Fig. 2,*C*) the distortion of the curve of the left anterior descending coronary artery assumed the gradually sloped V-curve. As normal rhythm resumed, the sharp V-shaped angular distortion could be visualized. Postmortem examination of the heart (Fig. 2,*D*) revealed a band of myocardial fibers, approximately 7 mm. in width, crossing over the left anterior descending coronary artery at a site 1 cm. distal from the place of the apical branch. The electrocardiograms taken of Dog No. 12 were at all times normal.

On the angiographic study of the second animal, Dog No. 13, made during acetylcholine arrest (Fig. 3,*C*), there is uniform filling of the left anterior descending coronary artery throughout, demonstrating the usual oxbow curve. The angiograms taken during the regular rhythm (Fig. 3,*A* and *B*), however, on occasional films show a small depression in the superior margin of the left anterior descending coronary artery at the site of emergence of the apical branch. This shallow depression is approximately 4 mm. in length and is only visualized transiently. Postmortem examination of the heart of this dog (Fig. 3,*D*) revealed a band of myocardial fibers, approximately 4 mm. in width, crossing over the left anterior descending artery just proximal to the site of origin of the apical branch.

Discussion

Myocardial bridges over the coronary arteries have been of interest since Geiringer's description[4] in 1951. Their relationship to coronary arteriosclerosis has been disputed. Polacek[7] believes that they play a role in the sclerotic process since he reports the existence of intimal hyperplasia proximal to these bridges, whereas the intima remains thin underneath the bridges. On the other hand, Edwards and associates[1] did not observe any difference between the sclerotic process in the "intramural" (underneath the bridge) and that in the "extramural" (epicardial) portions of the coronary arteries.

Disagreement also exists in regard to the frequency of occurrence of these myocardial bridges. Polacek[7] reports their presence in 85.7 per cent of 70 human hearts examined. Edwards[1] reports a frequency of 5.4 per cent in 276 hearts examined. In our small group of 23 dogs the 2 cases would represent a frequency of 8.7 per cent. Polacek[7] states that these bridges and loops occur frequently in dogs but reports no frequency. It should also be noted that no myocardial loops from the atrial musculature were observed in the present study. The possible role of myocardial loops producing local deformity of the proximal segment of the right coronary artery will be reported on in a subsequent study. The ability of myocardial bridges to distort the normal architecture of the coronary vascular angiographic pattern warrants bringing it to the attention of radiologists and others engaged in coronary angiography. Such distortion may resemble focal disease on angiograms. This has been alluded to previously by Porstmann and Iwig.[8] In addition to the lack of anatomic evidence in their report, their illustrations do not show the alterations observed in the present study. Although the transient nature of this distortion is usually evident in angiographic studies made during the regular rhythm, a spurious, more permanent appearance of distortion may be present on angiograms taken during acetylcholine arrest. It be-

comes evident that acetylcholine arrest makes correct interpretation more difficult and the single-film technique advocated by some investigators[8] may fail to specifically define this anatomic variant.

Summary

Coronary angiograms were obtained on 23 normal dogs. Postmortem examination of these canine hearts revealed that myocardial bridges over the coronary arteries were present in 2 animals. Distortion of the coronary artery angiographic outline at the site of the myocardial bridges may resemble the angiographic view of a focal disease process. This distortion was transient in nature on angiograms taken during the regular rhythm but it was persistent on films taken during acetylcholine arrest. The effects of the myocardial bridge on the coronary vascular angiographic pattern and its importance in interpretation of such studies warrants bringing it to the attention of coronary angiographers.

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"Body surface" potentials produced by the eccentric dipole in the heart wall of the nonhomogeneous volume conductor

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For many years, physicians interested in electrocardiography have been aided in the interpretation of body surface potentials by the consideration that these potentials are nearly equivalent to those which would be produced by the resultant cardiac dipole oriented in the homogeneous volume conductor.[1] Recent considerations[2-4] have emphasized the changes in these potentials which would result if the volume conductor were nonhomogeneous.

It is the purpose of this communication to compare body surface potentials of the homogeneous and of the nonhomogeneous volume conductor which are produced by the eccentric current dipole positioned arbitrarily in the "heart wall."

Method

Laboratory studies have been completed upon the homogeneous[7,8] and upon the nonhomogeneous[6] circular lamina. These studies served to establish the required boundary conditions for the solution of the potential in circular harmonic functions. It was then possible to pass to the corresponding spherical harmonic functions for the general solution in the nonhomogeneous spherical conductor. This general solution (Appendix I)[6] appeared in four equations. The last of these equations described the potential everywhere exterior to the heart, that is, on and between surfaces S_1 (heart surface) and S_2 (body surface) (Fig. 1). When the radius vector r of this equation is taken equal to R_2 (the body surface radius) one obtains the particular solution (see appendix) for the potential at every point on the body surface S_2.

All potentials are computed using this particular solution in the 1620 I.B.M. computer. Potentials due to the radial and to the tangential components of the dipole are computed separately (Tables I-III). It was thought to be instructive if the potentials computed were the result of three dipole positions. Thus, position 1 was taken 1 mm. exterior to the endocardial surface, S_1 of radius R_1. Position 2 was taken halfway between S_1 and the epicardial surface, S_2. Position 3 was taken 1 mm. internal to the epicardial surface, S_2 of radius R_2 (Fig. 1).

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The radius vector r_d from the heart center O to the dipole position is taken along the +Z-axis. At the terminus of r_d the dipole of moment M(=1Dρ_2/4π) is represented by three components $M\psi$ $M\psi$ and $M\psi$ which are parallel, respectively to the Z Y and X axes. The specific resistivities ρ ρ_2, and ρ_3 are those of the "heart cavity the heart wall and body tissue" exterior to the heart, respectively (Fig 1)

Results

The effect on the body surface potentials due to the specific resistivities appears in the values of the ratios (ρ_2/ρ_1) and (ρ_2 ρ) Table I gives the body surface potentials which are produced by a radial dipole component in each of the three positions and by the tangential component in the same three dipole positions. They are computed using the ratios (ρ_3/ρ = 1) (ρ_1/ρ_2 = 0 5) Columns 1 4 and 7 of Table II give the corresponding results for the homogeneous case with the radial dipole component $M\psi$ and columns 1 4 and 7 of Table III give the corresponding results for the homogeneous case with the tangential dipole component $M\psi$ Clearly Table I shows that increasing the specific resistivity of body tissue exterior to the heart produces an increase in the absolute magnitude of the body surface potentials. If the specific resistivity ρ of the tissue exterior to the heart wall is twice that (ρ_2) of the heart wall the maximal potential of the radial or the tangential component may be increased by 1 44 times. Moreover this increase appears to be *independent* of dipole position between the endocardial and epicardial surfaces

The effects on body surface potential which are produced by decreasing cavity resistivity are depicted by Tables II and III and by Figs. 2 and 3 The cavity effect are produced by the ratios (ρ ρ = 5 0) and (ρ ρ = 10 0) when the ratio (ρ_1 ρ = 0 5) retained throughout Here the outstanding effect a further increase in body surface potentials which are produced by the radial dipole component and an overall increase these potentials when produced by the tangential dipole component In comparison with the homogeneous case the former may be great as 3 14 times when the dipole is near the endocardium, and 2.31 times when the dipole is near the epicardium In comparison with the homogeneous case, reduction of the body surface potentials due to the tangential dipole component may be as great as 0 68 times when the dipole is near the endocardium and as little as 0 90 times when the tangential component is near the epicardial surface.

Of considerable interest is the fact that maximal potentials (θ = 0°) due to the radial dipole component (Table II columns 2 5 8 or 3 6, 9) decrease as this component moves from the endocardial

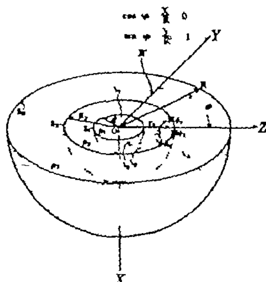
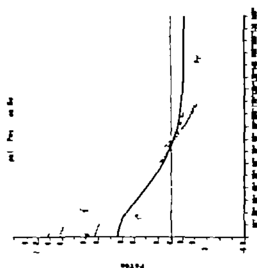
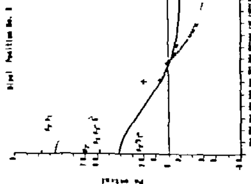


Fig 1 The center of the nonhomogeneous conductor is chosen for the origin O of the rectangular coordinate system X, Y Z. The surfaces S_1 S_2 and S are the endocardial, the epicardial, and the body surface, respectively The radii R R_2 and R are those of the heart cavity the heart, and the body respectively The specific resistivities ρ_1, ρ_2 and ρ_3 are those of the cavity the heart wall, and tissue exterior to the heart, respectively The radius vector is taken along the +Z-axis from O to point in the heart wall at which the arbitrary dipole is located. $M\psi_z$, $M\psi_y$, and $M\psi_x$ are components of the dipole parallel respectively to X, Y and Z. R is the projection of R_1 onto the XY plane. The position vector R_1 makes an angle θ with the Z-axis. The terminus of R_1 indicates the point at which the body surface potential is evaluated. A fictitious spherical surface passes through the dipole position. V is the potential anywhere in the cavity V anywhere in the heart wall interior to the fictitious surface, V anywhere is the heart wall exterior to the fictitious surface, and V is the potential anywhere exterior to the heart.





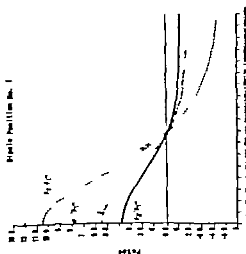
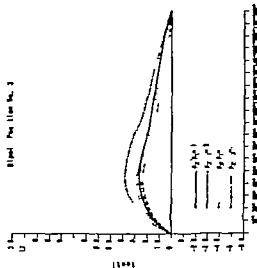
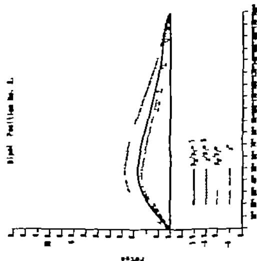


Fig. 2. (For legend see bottom of page 203.)





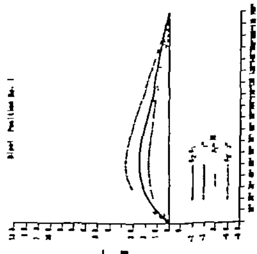


Fig. 3. (For legend see bottom of page 203.)

surface to the epicardial surface. Here the decreases in B ≠ 1 exceed the increases in (r_0/R) in the computed formula (see appendix). It is clear therefore that at points on the body surface *remote* from the heart, the peak of R *does not* necessarily signal the time of arrival on the subjacent epicardial surface of the accession process. However this particular argument is supported (Table II, columns 1, 4, 7) by the case of the homogeneous volume conductor.

On the body surface the zeros of the potential (Table II) make the dipole appear *less* eccentric than would be the case if the volume conductor were homogeneous. These findings make the potential of the weighted central terminal appear highly appropriate. The weighted central terminal requires that the arm resistances of the terminal be 2.6 times that of the left leg resistance. The change from equal resistances compensates for the proximity of the heart to the shoulder regions in comparison to the more remote pelvic-girdle region of the body trunk.[1]

In Tables I-III and in Figs. 2 and 3 the moment M has been arbitrarily chosen at the convenient magnitude of 100 Ma. cm. Consequently, once the arbitrary direction of M is chosen, its direction cosines ψ, ψ and ψ are known. When the tabulated potentials are multiplied by the appropriate direction cosines and summed, the body surface potential at the point in question is determined.

As a final step, the maximal values of the potential were computed for the limiting case $(\rho_3/\rho = \infty)$, $(\rho_2/\rho = 0.5)$. For the radial dipole component these were 12.34 for dipole position 1, 11.85 for dipole position 2, and 11.27 for dipole position 3. The body surface electrode position in all instances was at $\theta = 0°$. In the case of the tangential dipole component all maximal potentials were at $\theta = 40°$ and were 0.38, 1.33, and 2.04 for dipole positions 1, 2, and 3 respectively.

Discussion

The findings outlined above extend those which have been reported by others.[1-3] Nevertheless, the results permit rather limited clinical generalizations. During atrial accession dipole axis orientation is for the most part tangential. This may account for a decreased size of the P deflection. On the contrary, normal ventricular accession is depicted by an electromotive double-layer surface which expands in a radial direction. The over-all radial orientation of its dipole axes may be expected to produce an increased voltage in the QRS complex. The increase may be as much as threefold when compared with the homogeneous case and an increase of 3.7 fold when compared with tangential potentials in the nonhomogeneous case. On the other hand, accession of the last 0.04 second of a 0.12-second QRS complex is apt to be comprised of dipoles with axes which are more *tangential* than radial, and this will tend to minimize the magnitude of the associated QRS voltage. Increases of the specific resistivity, ρ_2, of body tissue exterior to the heart increase the body surface potentials. Dipole locations close to the heart cavity produce body surface potentials which are altered to a maximal extent by changes in the heart cavity resistivity, ρ_1. The decreased heart cavity resistivity of anemia may be expected to increase the QRS voltage in superjacent precordial leads. Moreover, the early QRS voltages of normal ventricular accession should show the greatest increases of voltage. Polycythemia increases the value of ρ_1 and may be expected

Fig. 2. Graphic representation of the body surface potentials produced by the radial dipole component Mψ for each of three dipole positions (see text). The solid line indicates the homogeneous case $(\rho_2/\rho_1 = 1)$, $(\rho_3/\rho_2 = 1)$. The dash-dot line indicates the case $(\rho_2/\rho_1 = 1)$, $(\rho_3/\rho_2 = 0.5)$. The dotted line indicates the case $(\rho_2/\rho = 3.0)$, $(\rho_3/\rho_2 = 0.5)$. The dashed line indicates the case $(\rho_2/\rho = 10.0)$, $(\rho_3/\rho_2 = 0.5)$. All curves are plotted from data given in Tables I and II.

Fig. 3. Graphic representation of the body surface potentials produced by the tangential dipole component Mψ for each of three dipole positions (see text). The solid line indicates the homogeneous case $(\rho_2/\rho_1 = 1)$, $(\rho_3/\rho_2 = 1)$. The dash-dot line indicates the case $(\rho/\rho_1 = 1)$, $(\rho_3/\rho_2 = 0.5)$. The dotted line indicates the case $(\rho_2/\rho = 3.0)$, $(\rho_3/\rho_2 = 0.5)$. The dashed line indicates the case $(\rho_2/\rho = 10.0)$, $(\rho_3/\rho_2 = 0.5)$. All curves are plotted from data given in Tables I and III.

Table I Body surface potentials produced by the radial and tangential components showing potential increases due to increase in resistivity of body tissue exterior to the heart

θ (degrees)	*Radial component* *($\rho_2/\rho_1 = 1$) ($\rho_2/\rho_1 = 0.5$)*			*Tangential component* *($\rho_2/\rho_1 = 1$) ($\rho_2/\rho_1 = 0.5$)*		
	Dipole position 1	*Dipole position 2*	*Dipole position 3*	*Dipole position 1*	*Dipole position 2*	*Dipole position 3*
0	5 52	5 87	6 26	0 00	0 00	0 00
10	5 28	5 59	5 93	1 27	1 40	1 53
20	4 64	4 85	5 07	2 35	2 54	2 76
30	3 74	3 84	3 93	3 10	3 30	3 53
40	2 77	2 77	2 77	3 51	3 68	3 86
50	1 84	1 79	1 74	3 64	3 75	3 87
60	1 03	0 95	0 88	3 57	3 62	3 68
70	0 34	0 27	0 20	3 36	3 38	3 38
80	−0 22	−0 28	−0 33	3 09	3 07	3 04
90	−0 66	−0 70	−0 74	2 78	2 73	2 69
100	−1 02	−1 04	−1 06	2 45	2 40	2 34
110	−1 30	−1 30	−1 30	2 12	2 06	2 01
120	−1 51	−1 50	−1 49	1 80	1 74	1 68
130	−1 68	−1 65	−1 63	1 48	1 43	1 38
140	−1 81	−1 77	−1 73	1 17	1 13	1 09
150	−1 90	−1 85	−1 80	0 87	0 84	0 81
160	−1 96	−1 90	−1 86	0 58	0 55	0 53
170	−2 00	−1 94	−1 89	0 29	0 28	0 26
180	−2 01	−1 95	−1 90	0 00	0 00	0 00
Column number	1	2	3	4	5	6

to produce an opposite effect on the QRS voltage. When the factors under discussion also produce significant changes in the radii of the heart cavity R_1 or heart wall R_2 either singly or in combination these effects must, according to Equations (1 7) enter the evaluation of the body surface potentials, particularly those on the torso at the heart level.

Finally it should be pointed out that the nonhomogeneous character of the conductor does not alter dipole moments but may increase or decrease the absolute magnitude of the potentials at all points in or on the surface of the volume conductor An increase in the specific resistivity of tissue exterior to the heart increases the body surface potential. Decreases in specific resistivity of the heart cavity content increases the body surface potentials when the dipole components are primarily radial in orientation and decreases these potentials when the components are primarily tangential in orientation

Addendum

More appropriate values for (ρ_2/ρ_1) and (ρ_2/ρ_3) have recently been received [13] These are 2 5 and 0 2 respectively for the nonhomogeneous case. Here a third thin shell of ratio ρ_3/ρ_4 (= 6 6) for the torso-shell exterior to the lungs, is neglected The general formula of the potential function may be easily adapted for an arbitrary number of nonhomogeneous shells.

Appendix

Given Equation (4) of the general solution for the potential everywhere in the nonhomogeneous spherical conductor produced by an arbitrary eccentric dipole in the heart wall we take r = R and have Equations (1 7) as shown at the bottom of page 205

In Equation (7) I is the current, D is the distance between the poles of the dipole, and ρ_2 is the specific resistivity of the heart wall. The first member on the right of Equation (1) is the potential due to the radial component $M\psi$ of the dipole. The second member on the right is the potential due to the two tangential dipole components $M\psi$ and $M\psi_x$.

The body surface potentials for the case of the *homogeneous* spherical conductor may be extracted from Equation (1) by taking $\rho_1 = \rho_2 = \rho$. Then $B = B = C = 1$ with the result shown in Equation (8)

For computation the assigned values are $M = 100$, $R_1 = 3.5$ cm, $R = 4.3$ cm., $R_3 = 12$ cm. and $r_0 = 3.6$ cm, 3.9 cm, and 4.2 cm for dipole positions 1, 2, 3 respectively. Inasmuch as r_0, the dipole eccentricity, is taken on the positive axis of Z, the Z axis becomes the polar axis of the sphere. The angle θ (Fig. 1) is permitted to vary from $\theta = 0°$ through $\theta = 180°$ as the radius vector R_3 moves over the longitude of the YZ plane. Here, $\sin\Phi$ varies from 0, +1 and 0. Clearly $\sin\Phi$ varies from 0, −1 and 0 as the terminus of R_3 moves over the longitude of the YZ plane, and θ varies from 180° through

(1)
$$V = \frac{M\Psi}{R_3^2}\sum_{n=1}^{\infty} B\ C_n (2n+1)\left(\frac{r}{R_3}\right)^{-} P\ (\cos\theta)$$
$$+\frac{M}{R^2}\left\langle\begin{matrix}\Psi\\ \Psi_x\end{matrix}\right\rangle\sum_{n=1}^{\infty} B\ C_n\left(\frac{2n+1}{n}\right)\left(\frac{r}{R_3}\right)^{-} P^1(\cos\theta)\left\langle\begin{matrix}\sin\Phi\\ \cos\Phi\end{matrix}\right\rangle \quad r = R_3$$

(2)
$$B = \left[1 + \frac{n+1}{n}\frac{\rho_2-\rho_1}{\rho_1\left(\frac{n+1}{n}\right)+\rho_2}\left(\frac{R}{r}\right)^{2n+}\right]$$

wherein

(3)
$$B = \left[1 - \frac{\rho_2-\rho_1}{\rho_1\left(\frac{n+1}{n}\right)+\rho_2}\left(\frac{R}{r}\right)^{2n+}\right]$$

and

(4)
$$C_n = \frac{2n+1}{n}\frac{R_3^{2n+}}{\alpha_n+\left(\frac{n+1}{n}\right)(\rho_2/\rho_3)\,\beta_n}$$

Also

(5)
$$\alpha_n = \left(R_3^{2n+1}+\frac{n+1}{n}R^{2n+}\right)$$

(6)
$$\beta_n = (R_3^{2n+} - R_3^{2n+})$$

and

(7)
$$M = ID\rho_2/4\pi$$

(8)
$$V = \frac{M\Psi}{R_3^2}\sum_{n=1}^{\infty}(2n+1)\left(\frac{r}{R_3}\right)^{-} P\ (\cos\theta)$$
$$+\frac{M}{R_3^2}\left\langle\begin{matrix}\Psi\\ \Psi_x\end{matrix}\right\rangle\sum_{n=1}^{\infty}\left(\frac{2n+1}{n}\right)\left(\frac{r}{R_3}\right)^{-} P^1(\cos\theta)\left\langle\begin{matrix}\sin\Phi\\ \cos\Phi\end{matrix}\right\rangle \quad r = R_3$$

*Table II Radial dipole component**

θ (degr)	Dipole position 1			Dipole position 2			Dipole position 3		
	m/m = 1 m/m = 1	m/m = 5 m/m = 0 5	m/m = 10 m/m = 0 5	m/m = 1 m/m = 1	m/m = 5 m/m = 0.5	m/m = 10 m/m = 0.5	m/m = 1 m/m = 1	m/m = 5 m/m = 0.5	m/m = 10 m/m = 0.5
0	3 83	10 55	12 04	4 08	9 67	10 79	4 35	9 19	10 07
10	3 66	10 14	11 58	3 88	9 26	10 35	4 12	8 8	9 63
20	3 20	8 99	10 30	3 35	8 17	9 16	3 51	7 66	8 44
30	2 58	38	8 49	2 64	6 65	7 50	2 71	6 14	6 81
40	1 89	5 60	6 47	1 90	4 99	5 67	1 89	4 53	5 07
50	1 25	3 85	4 48	1 21	3 39	3 89	1 17	3 02	3 43
60	0 68	2 26	2 67	0 63	1 96	2 29	0 58	1 71	1 98
0	0 22	0 89	1 09	0 16	0 74	0 91	0 11	0 60	0 74
80	−0 16	−0 26	−0 24	−0 20	−0 27	−0 25	−0 24	−0 30	−0 28
90	−0 46	−1 21	−1 36	−0 49	−1 10	−1 21	−0 52	−1 04	−1 13
100	−0 70	−1 99	−2 27	−0 72	−1 78	−2 01	−0 73	−1 64	−1 82
110	−0 88	−2 62	−3 02	−0 89	−2 33	−2 65	−0 89	−2 12	−2 38
120	−1 03	−3 12	−3 63	−1 02	−2 77	−3 17	−1 01	−2 51	−2 83
130	−1 14	−3 52	−4 11	−1 12	−3 12	−3 58	−1 10	−2 81	−3 18
140	−1 22	−3 83	−4 48	−1 20	−3 38	−3 90	−1 17	−3 04	−3 64
150	−1 28	−4 06	−4 76	−1 25	−3 58	−4 14	−1 22	−3 21	−3 67
160	−1 32	−4 22	−4 95	−1 29	−3 72	−4 31	−1 25	−3 33	−3 81
1 0	−1 35	−4 31	−5 07	−1 31	−3 80	−4 40	−1 27	−3 40	−3 89
180	−1 36	−4 34	−5 10	−1 32	−3 83	−4 44	−1 28	−3 42	−3 92
Zero	5 7°	77 8°	78 2°	74 5°	77 3°	77 8°	73 6	76 6	77 3°
Column number	1	2	3	4	5	6	7	8	9

*The potentials on the longitude of the sphere for dipole position 1 one millimeter exterior to the endocardium; for dipole position 2, halfway between the endocardial and epicardial surfaces; and for dipole position 3, one millimeter interior to the epicardial surface.

360° For the tangential component Mψ the YZ-plane is the zero-potential plane of the sphere wherein cos Φ is everywhere zero (Fig 1)

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Table III. Potentials on the longitude of the sphere in the YZ plane produced by the tangential dipole component in this plane and with dipole axis direction parallel to the positive Y-axis

θ (degrees)	Dipole position 1			Dipole position 2			Dipole position 3		
	$\rho_2/\rho_1 = 1$, $\rho_3/\rho_1 = 1$	$\rho_2/\rho_1 = 5$, $\rho_3/\rho_1 = 0.5$	$\rho_2/\rho_1 = 10$, $\rho_3/\rho_1 = 0.5$	$\rho_2/\rho_1 = 1$, $\rho_3/\rho_1 = 1$	$\rho_2/\rho_1 = 5$, $\rho_3/\rho_1 = 0.5$	$\rho_2/\rho_1 = 10$, $\rho_3/\rho_1 = 0.5$	$\rho_2/\rho_1 = 1$, $\rho_3/\rho_1 = 1$	$\rho_2/\rho_1 = 5$, $\rho_3/\rho_1 = 0.5$	$\rho_2/\rho_1 = 10$, $\rho_3/\rho_1 = 0.5$
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	0.89	0.61	0.42	0.98	0.91	0.77	0.08	1.17	1.07
20	1.64	1.12	0.77	1.78	1.64	1.38	1.93	2.08	1.89
30	2.15	1.47	1.00	2.30	2.10	1.75	2.46	2.61	2.34
40	2.43	1.66	1.12	2.55	2.29	1.90	2.68	2.79	2.47
50	2.51	1.72	1.14	2.59	2.29	1.85	2.67	2.72	2.38
60	2.45	1.68	1.11	2.49	2.17	1.73	2.53	2.53	2.18
70	2.30	1.59	1.04	2.31	1.99	1.56	2.31	2.27	1.94
80	2.10	1.46	0.95	2.09	1.78	1.38	2.07	2.01	1.69
90	1.88	1.32	0.85	1.86	1.57	1.20	1.82	1.75	1.45
100	1.66	1.17	0.75	1.62	1.37	1.03	1.58	1.50	1.23
110	1.43	1.02	0.65	1.39	1.17	0.88	1.35	1.27	1.04
120	1.21	0.86	0.55	1.17	0.98	0.73	1.13	1.06	0.86
130	1.00	0.71	0.46	0.96	0.80	0.60	0.92	0.86	0.69
140	0.79	0.57	0.36	0.76	0.63	0.47	0.73	0.68	0.54
150	0.58	0.42	0.27	0.56	0.47	0.35	0.54	0.50	0.40
160	0.39	0.28	0.18	0.37	0.31	0.23	0.36	0.33	0.26
170	0.19	0.14	0.08	0.18	0.15	0.11	0.18	0.16	0.13
180	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	2.51	1.72	1.14	2.59	2.29	1.90	2.68	2.79	2.47
Column number	1	2	3	4	5	6	7	8	9

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Effect of isoproterenol in "severe" experimental lung embolism with and without postembolic collapse

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Isoproterenol was shown to prevent some of the cardiorespiratory consequences of minor lung embolism In the first part of this paper the fate of the intravenously injected embolic material will be demonstrated in untreated and isoproterenol medicated animals. Subsequently the ability of isoproterenol to prevent the consequences of a single dose or of repeated large doses of embolic material will be shown

In addition to a demonstration of its prophylactic effect it seemed obviously important to assess to what extent isoproterenol can restore animals previously subjected to lung embolism. Animals both with and without postembolic collapse have been investigated

Methods

Forty two sheep which ranged in weight from 29 to 48 kilograms, were used. The fasting supine animals were anesthetized with thiopentone and intubated. The femoral veins and arteries and the forelimb veins were dissected free.

Measurements of circulation. Cardiac catheters were passed via the femoral veins into the right atrium and into the pulmonary artery A cannula was introduced into the femoral artery and polyethylene catheters into the forelimb veins.

Oxygen saturation of the arterial and mixed venous blood and hemoglobin content were measured spectrophotometrically[2] Oxygen uptake tidal volume and rate of breathing were measured from the record obtained by a twin spirometer (Pulmotest†) while the animal breathed air

Samples of blood were taken in the mid period of measurements of ventilation. The Fick principle was used to calculate pulmonary arterial blood flow and the shunt formula ($Cc_{O_2} - Ca_{O_2}/Cc_{O_2} - C\bar{v}_{O_2}$) was used to calculate venous admixture as per

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cent of cardiac output. Venous admixture measured in this way represents the sum of vascular and alveolar right-to-left shunts. Oxygen content of the pulmonary capillary blood (Cc_{O_2}) was estimated by subtracting 0.60 volume per cent from the oxygen-carrying capacity of the arterial blood[4]; that of the arterial (Ca_{O_2}) and mixed venous ($C\bar{v}_{O_2}$) bloods was calculated by multiplying the oxygen-carrying capacity with the corresponding values of saturation.

Pulmonary arterial, femoral arterial, and right atrial pressures were measured with Sanborn transducers and recorded on a multichannel direct writing oscillograph and expressed in millimeters of mercury. Total pulmonary and systemic resistances were calculated by the usual formulas and expressed in dynes-sec.-cm^{-5}.

Blood flows, resistances, and ventilated volumes were expressed on the basis of liters per square meter of body surface area (BSA).

INTRAPLEURAL PRESSURE. This was measured via a specially prepared 17-gauge needle introduced into the third or fourth intercostal space. A pneumothorax of 60 to 100 ml. was induced. The needle was connected to a Sanborn transducer. Intrapleural pressure was recorded relative to atmosphere in centimeters of water.

AIR FLOW RATE AND TIDAL VOLUME. These were obtained by the Godart pneumotachometer and integrator.* Intrapleural pressure, air flow, and tidal volume were electrically amplified and recorded simultaneously on the oscillograph.

Method of analysis. Lung compliance expressed in milliliters per centimeter of water per kilogram was obtained by dividing the tidal volume by the simultaneously recorded intrapleural pressure between points of zero flow and dividing the result by the body weight of the animal expressed in kilograms.

Details of these techniques are described elsewhere.[4,5]

Inflation of lungs. In the majority of these experiments, inflation of the lungs was performed by using a Royal Melbourne resuscitator† with a pressure of 30 mm. Hg.

Embolic material. A dose of 0.20 ml. per kilogram of a 33 volume per cent barium sulfate emulsion was injected into the pulmonary artery or into a forelimb vein.

Preparation of labeled barium sulfate. Radioactive serum albumin I^{131}* was added to a 10 per cent suspension of barium sulfate in normal saline and incubated at 66°C. for 60 minutes. The material was washed once with sheep plasma and twice with normal saline. The final precipitate was reconstituted with normal saline to the usual concentration. The label was moderately stabile but there was some elution of the albumin on incubation at 37°C. The injected material contained 2 per cent of the radioactivity in the supernatant.

A medical probe† with a flat-field collimator and rate meter 1620 BS whose modified output was recorded simultaneously with the pressures on the oscillograph were used to measure activity over the right lower lobe with the chest intact.

Between 10 and 20 microcuries was injected. Arterial samples were taken every 20 seconds after the injection of the barium. When the animals were sacrificed some hours after the last injection of the labeled material, 1-gram pieces of lung were taken from various regions and counted in a well scintillator counter.‡

Statistical methods were used as recommended by Snedecor.[6]

Autopsy. After the experiment the animals were sacrificed with an overdose of thiopentone, the lungs were removed, and all lobes were cut across and inspected for edema.

Groups. Labeled barium sulfate was injected into 2 sheep. First, 0.02 ml. per kilogram of a 33 volume per cent barium sulfate was administered and the changes were recorded continuously. Thirty minutes later a continuous infusion of 0.33 μg per kilogram per minute of isoproterenol hydrochloride (Isuprel, Winthrop) was started and a dose of 0.04 ml. per kilogram of barium sulfate was injected.

A continuous intravenous infusion of 0.33 μg per kilogram per minute of isoproterenol was administered in 9 sheep

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†Commonwealth Industrial Gases, Ltd., Sydney, Australia.

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†Nuclear Chicago, DS-201.
‡Nuclear Chicago, DS-202.

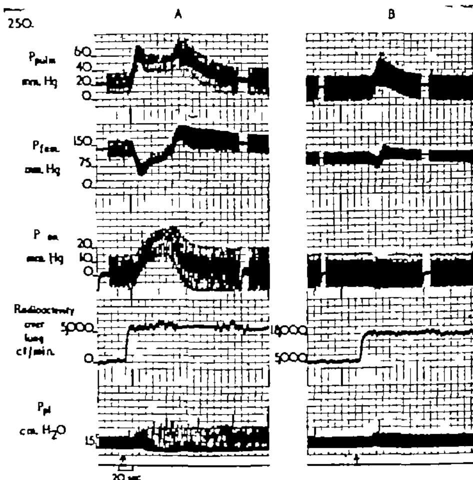


Fig. 1. Simultaneous measurement of radioactivity over lung and pressures after the intravenous injection of barium sulfate. A, 0.02 ml./Kg. of barium sulfate during control period. B, 0.04 ml./Kg. of barium sulfate during intravenous infusion of isoproterenol. The arrows indicate injection of embolic material.

Control measurements were followed by the intravenous injection of the standard dose (0.20 ml. Kg.) of embolic material. Pressures were recorded continuously; other measurements were repeated 5 minutes later. Subsequently the lungs were inflated and lung compliance again determined. This in 3 animals was followed by a 5-minute period of inhalation of isoproterenol-aerosol (Neo-epinine, Burroughs Wellcome, 0.5-1.0 per cent solution). The aerosol was administered with a Mark 8 Bird respirator* using an inflating pressure of 20 cm. H_2O and four to six inspirations at a pressure of 40 cm. H_2O. After this period measurement of lung compliance was repeated.

*Bird Corporation, Palm Springs, Calif.

In 3 animals of the above-mentioned group infusion of isoproterenol was continued and the same dose of embolic material was injected at intervals of 5 to 7 minutes until the animal died. Measurements were repeated after each dose.

The standard dose of barium sulfate was injected in 11 sheep (untreated) and was followed by inflation of the lungs. Measurements were then taken and catecholamines were given subsequently. A continuous intravenous infusion of isoproterenol (0.33 µg/Kg./min.) was administered in 4 sheep; in 2 animals the infusion consisted of 0.40 and 2.0 µg/Kg./min. of epinephrine, respectively; in 2 animals, 0.50 and 0.40 µg/Kg./min. of norepinephrine was infused. During the infusions the lungs were inflated and the measurements repeated.

Three sheep were subjected to a 5-minute period of inhalation of isoproterenol as described before and the measurements were repeated after the inhalation had been discontinued.

In 20 untreated animals the injection of the second or third standard dose of barium sulfate resulted in severe systemic hypotension and apnea. Three animals were left untreated. 3 were given 6 to 10 μg/kg of norepinephrine intravenously. 3 were given val[5] Hypertensin II-asp-β-amide (Hypertensin Ciba) in the form of a continuous intravenous infusion (1 to 8 μg kg min.) or repeatedly as single injections (20 μg/kg.). 11 sheep were given isoproterenol as a continuous intravenous infusion (0.33 μg kg min.) or as a single intravenous injection (3 to 5 μg kg.). Inflation of the lungs was performed in all animals.

Results

Fate of injected barium sulfate. The record of the surface counts over the lung both during the control period and when the animal was protected with isoproterenol shows that no significant amount can have escaped from the lung (Fig. 1). This was confirmed by the serial arterial samples in which a trace of barium was detected in the first four samples, representing less than 1 per cent of the injected material.

There was a time lag of from 10 to 12 seconds between the arrival of the particles in the lung and the rise in pulmonary arterial pressure. Although the pulmonary arterial pressure gradually returned to normal, radioactivity over the lung remained unchanged during the entire period of observation (30 minutes).

The response of pulmonary arterial pressure to the injection of barium sulfate during the continuous infusion of isoproterenol was considerably reduced and so was the fall in systemic arterial pressure. The pulmonary uptake of the particles was, however, as complete as in the control period.

The samples of lung obtained at autopsy showed a considerable variation in the amount of retained activity. A hemorrhagic sample from the posterior part of the lower lobe contained 4,400 counts per gram, whereas a sample from the lingular lobe, which was normal in appearance, contained 1,000 counts per gram.

Effect of standard dose of barium sulfate during infusion of isoproterenol (Table I). The administration of isoproterenol caused a gross rise in cardiac output, ventilation and rate of breathing as shown by the high starting values. Embolism was followed by a significant increment in systemic and pulmonary arterial pressures, pulmonary arterial resistance, and venous admixture. Ventilation and right atrial pressure remained unchanged. There was a statistically significant fall in arterial oxygen saturation and lung compliance. The immediate rise in pulmonary arterial pressure in the untreated and isoproterenol-medicated sheep is shown in Fig. 2.

In the isoproterenol treated group, the embolism-induced rise in pulmonary arterial resistance, the ventilatory response and the fall in lung compliance were statistically significantly less severe than in the corresponding untreated group. The rise in pulmonary arterial pressure was not statistically significantly different ($0.05 < p < 0.10$).

The increment in lung compliance after

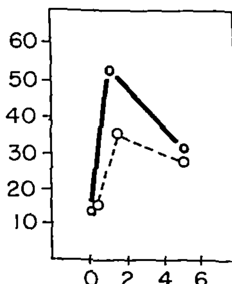


Fig. 2. Average values of the mean pulmonary arterial pressure before (O) and at 1 minute and 5 minutes after the injection of 0.20 ml./kg. of barium sulfate in the untreated (*solid line*, 6 animals) and isoproterenol-treated (*dotted line*, 9 animals) sheep. Abscissa: time in minutes; ordinate: pressure in mm. Hg.

Table I Cardiorespiratory response to lung embolism during infusion of isoproterenol

Parameter	Embolism	Group: Untreated controls (6 animals)	Group: Infusion of isoproterenol (9 animals)
Cardiac output (L./min./M.²BSA)	B	3 12	5 22
	A	2 87	5 47
Femoral arterial mean pressure (mm. Hg)	B	123	75
	A	135	87
Systemic arterial resistance (dynes-sec.-cm.⁻⁵/M. BSA)	B	3 289	1 203
	A	4 014	1 324
Pulmonary arterial mean pressure (mm.Hg)	B	13	15
	A	32	28*
Pulmonary arterial resistance (dynes-sec.-cm.⁻⁵/M. BSA)	B	344	233
	A	896	426*†
Arterial oxygen saturation (%)	B	91 6	86 1
	A	81 7*	79 8*
Venous admixture (% of cardiac output)	B	13	25
	A	31	37*
Ventilation (L./min./M.²BSA, BTPS)	B	6 4	18 5
	A	11 7	17 9†
Breathing rate (per min.)	B	30	56
	A	48*	59†
Tidal volume (ml./M.²BSA, BTPS)	B	219	334
	A	253	309
Lung compliance (ml./cm. H_2O/kg.)	B	3 49	2 63
	A	75	1 31*†
	I	1 51	2 06

*Difference from control period (B) significant (p <0.05).
†Difference in response significant from untreated controls (p <0.05).
Before (B) and 5 minutes after (A) embolism. I After inflation of the lungs.

the forced inflation of the lung was statistically significant The postinflation value of lung compliance was not statistically different (0 10 < p <0 20) from the control measurement.

Effect of repeated emboli during infusion of isoproterenol A representative pair of experiments is shown in Fig 3 Repeated emboli caused a gradual decline in cardiac output and femoral arterial pressure and resistance Mean pulmonary arterial pressure was, on the average 48 mm. Hg in untreated animals after the second embolus the average corresponding value in the isoproterenol-treated sheep was 28 mm. Hg and the level of 50 mm. Hg was reached only after the sixth or seventh embolus. Pulmonary arterial resistance in the untreated animals rose, on the average to 1 600 dynes-sec.-cm.⁻⁵ per square meter of body surface area after the second embolus in the isoproterenol-treated sheep the average value of pulmonary resistance was 1 300 after the sixth or seventh embolic episode. The difference in lung compliance was less striking in these sheep. After the second embolus it amounted on the average to 16 per cent of the control value in the untreated animals and 28 per cent in the isoproterenol treated sheep. After the sixth embolus the average value of lung compliance in the isoproterenol medicated group was 16 per cent. Arterial oxygen saturation after the second embolus was, on the average 47 per cent in the untreated sheep the corresponding figure in the medicated group was 82 per cent and remained around this level after the consecutive embolic episodes.

The third embolus was invariably fatal in all untreated sheep some even died after the second One of the isoproterenol treated animals tolerated eight embolic episodes, the other 2 tolerated six.

Effect of catecholamines administered after embolism

A. ANIMALS WITHOUT POSTEMBOLIC COLLAPSE (TABLE II) The intravenous administration of isoproterenol after embolism resulted in a fall in systemic and pulmonary arterial pressures and resistances and a rise in arterial oxygen saturation tidal volume, and lung compliance ventilation remained virtually unchanged. Isoproterenol administered as an aerosol resulted in similar changes.

Only one of the 2 animals treated with infusion of epinephrine had an elevated pulmonary arterial pressure this showed a slight reduction. The administration of both epinephrine and norepinephrine caused a rise in systemic arterial pressure and resistance and some decrease in ventilation. Cardiac output increased only after the small dose of epinephrine Arterial oxygen saturation increased after epinephrine and remained unchanged after the administration of norepinephrine. In these cases there was very little change in lung compliance.

B. ANIMALS WITH POSTEMBOLIC COLLAPSE.

1. Untreated animals The onset of pulmonary hypertension was followed within 2 to 4 seconds by a fall in systemic arterial pressure. As systemic arterial pressure reached its lowest value, bradycardia commenced and pulmonary arterial pressure declined. Approximately 6 to 10 seconds after the onset of pulmonary hypertension a rapid rise in right atrial pressure occurred. Within 60 to 80 seconds after embolism, pressures in all these three segments of the circulatory system became about equal (30 to 35 mm. Hg) The rise in the intrapleural pressure swing followed the onset of pulmonary hypertension within 2 to 4 seconds, and within approximately 80 to 100 seconds after embolism the animal was apneic. Repeated inflation of the lung failed to restore spontaneous breathing

Table II *Effect of the administration of catecholamines after lung embolism*

Substance administered		*Isuprel*	*Neo-epinine*	*Epinephrine*	*Epinephrine*	*Norepinephrine*
Route		*Venous*	*Inhalation*	*Venous*	*Venous*	*Venous*
Dose (microgram/Kg.)		*0.33/min*	*40.0*	*0.40/min.*	*2.0/min.*	*0.40/min.*
Number of animals		*4*	*3*	*1*	*1*	*2*
Cardiac output	C	3 82	3 66	3 15	4 92	4 42
(L./min./M BSA)	T	4 22	4 56	5 82	4 88	4 67
Femoral arterial mean	C	83	111	110	115	107
pressure (mm. Hg)	T	67	69	140	155	L.6
Systemic arterial resistance	C	1 728	2 746	2 905	2 159	1 937
(dynes-sec.-cm.$^{-5}$/M.^{2}BSA)	T	1 277	1 139	2 000	2 952	2 158
Pulmonary arterial mean	C	20	32	24	13	27
pressure (mm. Hg)	T	15	17	21	14	4
Pulmonary arterial resistance	C	412	771	633	246	499
(dynes-sec.-cm.$^{-5}$/M. BSA)	T	299	323	300	267	411
Arterial oxygen	C	77 7	80 1	64 2	46 7	66 9
saturation (%)	T	91 2	88 2	79 8	67 8	68.7
Venous admixture	C	33	34	61	67	47
(% of cardiac output)	T	11	20	64	59	45
Ventilation	C	17 9	18 7	17 2	25 2	18 7
(L./min./M.^{2}BSA)	T	18 6	22 5	13 3	19 0	18 2
Breathing rate	C	57	73	56	76	82
(per min.)	T	56	69	52	64	75
Tidal volume	C	321	253	307	210	230
(ml./M.^{2}BSA)	T	342	323	256	162	244
Lung compliance	C	1 62	2	1 85	42	78
(ml./cm.H_2O/Kg.)	T	4 30	1 73	1 88	.53	90

C Control period (after embolism plus inflation of lung) T During treatment after repeated inflation of lung.

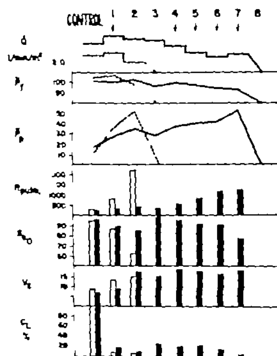


Fig 3 The effect of repeated injections of 0.20 mL/kg of barium sulfate (as indicated by arrows on top) in an untreated (dotted line white columns) and isoproterenol-treated (solid line black columns) sheep The untreated animal died after the third injection. $\dot{Q}$ Cardiac output $\bar{P}_f$ and $\bar{P}_p$ Femoral and pulmonary arterial pressures (mean, mm.Hg). Sa_{O_2} Arterial oxygen saturation (per cent). R_{pul} Pulmonary arterial resistance (dynes-sec.-cm.$^{-5}$/M BSA) $\dot{V}$ Ventilation (L./min./M BSA). C_L Lung compliance per cent of control value

These changes were identical in all the 20 sheep investigated in this way During the following 2 to 3 minutes in the 3 sheep which did not receive treatment at this stage, all pressures gradually declined and within 5 to 6 minutes after the embolic episode the animals were dead

2 Effect of administration of isoproterenol Isoproterenol either as a single injection or as a constant intravenous infusion resulted in a prompt response in 9 of 11 animals The response (Figs. 4 and 5) can be divided into three stages. The main event during the first stage—the first 60 to 90 seconds after injection—was the resumption of spontaneous breathing The animals, formerly unresponsive to repeated inflations of the lungs, resumed breathing after a single inflation At the same time there was a gradual increase in the pulmonary arterial pulse pressure The second stage (the next 40 to 50 seconds) was characterized by a rapid rise in the systemic arterial pressure which resulted in an overshoot and was accompanied by a corresponding fall in right atrial pressure pulmonary arterial pressure gradually increased. During this stage there was a marked hyperventilation A gradual decline in the pulmonary and systemic arterial pressures was observed in the third stage systemic arterial pressure soon reached control level while pulmonary arterial pressure remained slightly elevated Cardiopulmonary parameters determined at this time were comparable to those obtained in the isoproterenol treated group without postembolic collapse. In 2 cases the administration of the drug was ineffective in one of these the injection was given 6 minutes after embolism.

3 Effect of administration of norepinephrine and Hypertensin None of the 6 animals responded to these drugs the course and outcome of their condition was identical to those of the untreated sheep. They were in the same state and the drugs were given in each case at the same time as in those which responded to isoproterenol

Macroscopic appearance of the lung Scattered foci of atelectasis and hemorrhage were the usual finding Evidence of lung edema could only be obtained in some cases of repeated embolism in which a small amount of foam could be expressed from the cut surface of the lung in some areas.

Discussion

The average size of barium sulfate particles amounts to 25 microns.[7] Approximately all of the microspheres between 1 4 and 2.0 microns in diameter go through the pulmonary circuit in dogs, but only a few of those larger than 8 microns are found in the systemic circulation [8] Therefore a small degree of nonuniformity would theoretically enable numerous barium sulfate particles to pass the lung capillaries. Gross and Brown have demonstrated that most particles injected into the blood stream are immediately coated with plasma protein and agglutinated This reaction is most likely to be responsible for the virtually complete retention in the lung of barium sulfate. The administration

of isoproterenol reduced the pulmonary hypertensive response but did not affect the retention of the particles. This is regarded as a further indication of the importance of a functional component in postembolic pulmonary hypertension. The remaining effect appears to be consistent with the mechanical blockade of the pulmonary vascular bed.

At 5 minutes after embolism the pres-

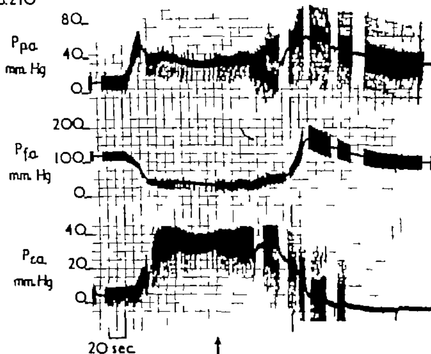


Fig. 4. Effect of lung embolism (at paper speed signal) and of the subsequent injection of 5μg/kg of isoproterenol (*at arrow*) on pulmonary and femoral arterial and right atrial (P_{ra}) pressures in sheep. Continuous segments in pressure record are electrical means. Note the rapid equalization of pressures in all three circuits after embolism and the prompt changes that follow the injection of isoproterenol.

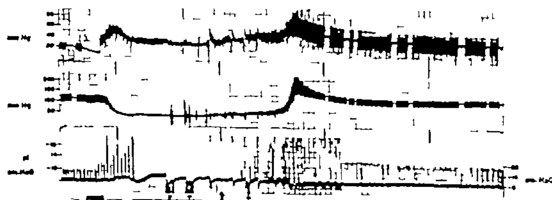


Fig. 5. Effect of lung embolism (*at black rectangle*) and of the subsequent infusion of isoproterenol (*begun at arrow*) in sheep. Embolism was followed by apnea, and repeated inflations of the lung (*asterisks*) remained ineffective. One single inflation after the infusion of isoproterenol (*third asterisk*) restored spontaneous

sures in the pulmonary and systemic circulations were fairly stable—cardiac output has been previously demonstrated to be unchanged between 5 and 30 minutes.[1] This appears to indicate that the application of the Fick principle was not unjustified in these experiments.

Isoproterenol was less effective in protecting than in restoring animals from the effects of a major embolic episode. The cause of this difference has been revealed by current experiments and will be discussed in a subsequent publication. The administration of the drug after embolism in animals with a maintained systemic arterial pressure was equally beneficial when given intravenously or by inhalation. The infusion of epinephrine was less effective, and that of norepinephrine had hardly any effect. However, in no case have we observed any rise in pulmonary arterial pressure or resistance during the infusion of any of these three catecholamines.

These findings are at variance with repeated suggestions (for references see Reference 1) that adrenergic stimuli contribute to the genesis of postembolic pulmonary hypertension. According to the present concept, the vessels contain two types of receptors for catecholamines, excitatory (α) and inhibitory (β). Epinephrine affects both, norepinephrine stimulates the α-type, isoproterenol acts on the β-type. It would appear that the pulmonary vasodilator activity of catecholamines in pulmonary embolism is related to their effect on the β-type of adrenergic receptors.

There was a considerable variation in the radioactivity of different portions of the lung after the injection of labeled barium sulfate during infusion of isoproterenol. This appeared to suggest that the pulmonary hypotensive effect of isoproterenol after embolism is not due simply to the abolition of perfusion inequality in the lungs. The present data, however, are not sufficient for a final conclusion.

Mechanism of death. The onset of pulmonary hypertension in all cases preceded systemic hypotension; the rise in right atrial pressure represented a mirror image of the changes in systemic arterial pressure. This suggested that the basic lesion in these animals was the obstruction of the pulmonary circulation. This obstruction was apparently so extensive that the flow of blood through the lung decreased sufficiently to cause systemic collapse and a fall in pulmonary arterial pressure. Since apnea was secondary to circulatory failure (see later), the maintenance of circulation was responsible for survival of multiple embolism during infusion of isoproterenol. The outstanding feature of these isoproterenol-treated animals, compared with controls, was the smaller increase in pulmonary arterial pressure and resistance. Since death in the controls could be related to pulmonary vascular obstruction, it is likely that the beneficial effect of isoproterenol was due mainly to its pulmonary vasodilator action, although a positive inotropic effect would also aid survival.

This interpretation is consistent with the absence of any beneficial effect derived from the injection of Hypertensin or norepinephrine and with the rise in systemic pressure after the injection of the vasodilator isoproterenol.

The sudden rise in central venous pressure is reminiscent of similar changes obtained by clamping of the pulmonary artery.[11] At this stage, pressures in all three circuits would represent the "static pressure"[12] of the entire system. The height of this static pressure is partly determined by vasoconstriction, since in the dying animal the static pressure declined.

Apnea always followed systemic vascular collapse. This is consistent with the prior conclusion[13] that severe hypoxia of the central nervous system induced by the cessation of the circulation is responsible for respiratory arrest. However, the role of respiratory reflexes in the mechanism of postembolic apnea would deserve careful attention.

Lung compliance. The fall in lung compliance after the injection of a large dose of barium sulfate was significantly reduced by a continuous infusion of isoproterenol. The administration of epinephrine and norepinephrine was ineffective.

Anesthetized animals show a tendency to breathe at a fixed tidal volume (i.e., constant transpulmonary pressure swing). If the fall in lung compliance is due to reversible causes, compliance is expected to remain unchanged even after the removal of the stimulus, until a large inflation is

performed. The duration of the stimulus or the beneficial effect of any intervention can, therefore, be judged only by the ability of inflation to restore lung compliance. If the stimulus continues to act compliance will remain depressed even after inflation.

Inflation of the lungs after the administration of isoproterenol restored lung compliance to near control level. This is consistent with the marked airway-dilator activity of isoproterenol There was some indication that the incomplete effect of this drug in some of the animals was due partly to insufficient local concentration since additional aerosol treatment resulted in a further improvement in lung compliance. However lung compliance even in these cases was not completely restored. Residual factors not reversed by isoproterenol which may be responsible for the fall in compliance include alterations of surface tension due to nonperfusion and alveolar edema (not evident to gross inspection) Catecholamines have been suggested as primarily involved in the pathogenesis of lung edema after microembolism.[14] However in dogs, pulmonary edema has been more frequent after partial sympathectomy or prior treatment with hexamethonium.[15] If lung edema participated in the genesis of the embolism induced fall in lung compliance[16] in our animals, the infusion of catecholamines appeared to inhibit edema rather than contribute to its development.

The infusion of isoproterenol prevented the postembolic rise in ventilation. This could have been due to the already high level of ventilation and to the reduced pulmonary circulatory changes resulting in a lesser stimulus to intrapulmonary receptors.

Ventilation perfusion relationship Venous admixture induced by the injection of barium sulfate was not affected by the continuous infusion of isoproterenol However the injection or the inhalation of the drug after the embolic episode resulted in a substantial increase in arterial oxygen saturation and in a corresponding fall in venous admixture. Two factors seemed to contribute to this effect. an increase in the number of ventilated alveoli (which meant a rise in lung compliance) and an improved perfusion of the alveoli caused by pulmonary vasodilatation and increment in blood flow Arterial oxygen saturation also improved after the injection of epinephrine after a dose of 0 4 μg per kilogram per minute this appeared to be due mainly to the increase in blood flow (which meant a rise in the oxygen saturation of the mixed venous blood) since lung compliance and venous admixture remained unchanged and after a dose of 2.0 μg per kilogram per minute there was a small decrement in venous admixture. The absence of any improvement in arterial oxygen saturation and venous admixture after the injection of norepinephrine is consistent with this substance s known lack of bronchodilator or pulmonary vasodilator activity [17]

The opening of arteriovenous shunts has been suggested as the cause of arterial hypoxemia in experimental lung embolism [1] In these experiments, as well as in our previous ones,[1] hypoxemia, as measured by the venous admixture, was related to lung compliance. When lung compliance increased, arterial oxygen saturation also improved and when lung compliance failed to increase, arterial oxygen saturation showed little change or was associated with increased cardiac output but no change in venous admixture. It has been claimed[18] that reduced arterial oxygen saturation was not due to bronchoconstriction because it was not abolished by hyperventilation with air This argument, however is not valid Since the fall in compliance represents the exclusion of part of the lung from ventilation hypoxemia is not likely to be relieved unless the changes in lung mechanics are reversed hyperventilation alone would be ineffective and with reversal of changes in compliance, unnecessary

Isoproterenol is the first substance with a proved beneficial effect in experimental lung embolism Its action is not restricted to barium sulfate embolism, and the changes in barium sulfate embolism are not unique to sheep. Although the dog appears to show less severe reactions than the sheep, the changes in lung mechanics have, for instance, been described in dogs. The amount of isoproterenol used in these experiments was within the human therapeutic range. Norepinephrine is currently used[19] in clinical medicine to combat post embolic collapse the unconvincing results

of this form of treatment are consistent with our observations. We suggest, therefore, that isoproterenol rather than norepinephrine should be considered for use in the emergency treatment of acute severe pulmonary embolism.

Summary

The pulmonary hypertension and the fall in lung compliance that follow the intravenous administration of a large dose of barium sulfate emulsion in sheep were significantly reduced by the injection of isoproterenol. The tolerance of sheep to repeated emboli was markedly increased by the continuous infusion of isoproterenol. The protective effect of the drug was less marked than its curative action. In severe postembolic collapse with apnea unrelieved by the administration of pressor substances (norepinephrine and Hypertensin) the injection of isoproterenol promptly restored 9 out of 11 animals.

In the intact sheep the pulmonary uptake of injected barium sulfate was virtually complete; this function was unaffected by the administration of isoproterenol.

It is suggested that the beneficial action of isoproterenol in experimental lung embolism is due mainly to stimulation of the β-type of adrenergic receptors resulting in a rise in cardiac output and in pulmonary vasodilatation.

Addendum

Two patients who presented with symptoms of severe lung embolism were given isoproterenol by Dr. J. C. Richards at the Royal Prince Alfred Hospital in Sydney. The treatment was ineffective. At autopsy, massive embolic occlusion of the pulmonary arterial trunk was found in both. This finding is consistent with those reported by Dexter and associates (Fourth World Congress of Cardiology, 1962, Mexico City, Abstracts, p. 102) showing that pulmonary vasoconstriction only occurs in cases of smaller sized emboli.

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Further observations with the normalized electrocardiogram and axis map

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A new method of electrocardiographic recording and analysis in three dimensions has recently been described in which the final records are electrocardiograms rather than vectorcardiograms.

In this method an orthogonal lead system was systematically rotated about three axes to the position at which the form of its three leads represented the closest possible match with a predetermined pattern. These rotations of the lead system about the heart were the equivalent of rotations of the heart within a fixed lead system. The rotations were accomplished by relatively simple electronic instrumentation.

The predetermined pattern of electrocardiographic deflections was one in which deflections in one lead were maximum, in a second minimum, and in the third lead equally negative and positive. This pattern was chosen because it provides approximate measures of the mean axes of QRS and T (i.e., of the direction of $\bar{\lambda}_{QRS}$ and $\bar{\lambda}_T$) and of the peak magnitude of the heart vector during these complexes. It also provides approximate measures of the area of QRS and T loops and of the extent to which the direction of the heart vector varies from a single direction and from a plane.

The procedure of rotations was entitled "normalization" of the electrocardiogram. Rotations of the lead system necessary to achieve the normalized form of the electrocardiogram were displayed as "axis maps" on which two of the three angles of rotation were indicated as the vertical and horizontal coordinates of a point, and the third by the inclination of a vector at that point. The coordinates of the point reflected the approximate mean axes of QRS and T in the same fashion that the latitude and longitude of a city represent its location on the surface of the earth. The inclination of the vector was a measure of the inclination of the plane of motion of the heart vector to a line of constant latitude.

As in the conventional electrocardiogram, the normalized electrocardiogram is a record of voltage plotted against time. It is, therefore, applicable to the recognition of cardiac rhythm and the measurement of intervals as well as providing the quantitative indices which have been described. Nine electrodes are used in the lead system.[1] The normalization procedure

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is straightforward. The electronic circuits can be incorporated into or attached to the clinical electrocardiograph.[2]

Application of this method of electrocardiographic analysis to a small group of normal subjects and a group of patients with a variety of electrocardiographic abnormalities has shown a striking separation of the groups on the basis of the axis maps alone.[1]

In the present study, the method of normalization has been applied to a larger number of normal subjects and to patients with the specific abnormality of left ventricular enlargement. The primary aim of the study was to evaluate further the method as a diagnostic aid rather than to develop new criteria for the diagnosis of left ventricular enlargement.

Materials and methods

Fifty normal subjects in the age range of 25 to 75 years and an equal number of patients with left ventricular enlargement in the age range of 30 to 75 years were studied. Medical history, physical examination, chest roentgenogram, and routine 12-lead electrocardiograms were obtained on all subjects. Subjects classified as normal had no evidence of cardiovascular disease. All patients were considered to have left ventricular enlargement, with roentgenographic evidence of this lesion and cardiovascular disease of a type appropriate to result in such enlargement. The entities considered to be responsible for enlargement were arterial hypertension, aortic stenosis, aortic insufficiency, and mitral insufficiency.

Normal electrocardiograms were obtained using the orthogonal lead system[3] and three-knob resolver[2] previously reported. Rotation of the system about its y axis was first carried to the position at which the QRS complex in the Z lead was initially negative and then equally positive, and the principal QRS deflection in the X lead was positive. This rotation was designated θ_n. A second rotation was carried out around the reoriented z axis to yield positive and negative QRS deflections in the Y lead. This rotation was designated ϕ. A third rotation designated δ was carried out around the twice reoriented x axis to the position at which the smallest possible triphasic or quadriphasic deflection occurred in the Y lead. Final leads containing normalized QRS

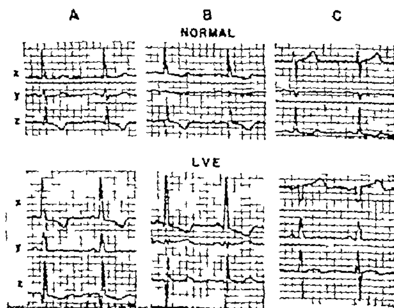


Fig. 1. Records from normal subject and patient with left ventricular enlargement. Records in column A are unrotated XYZ leads. Column B shows records from the same subjects in which the QRS complex has been normalized, and column C shows records in which the T wave has been normalized.

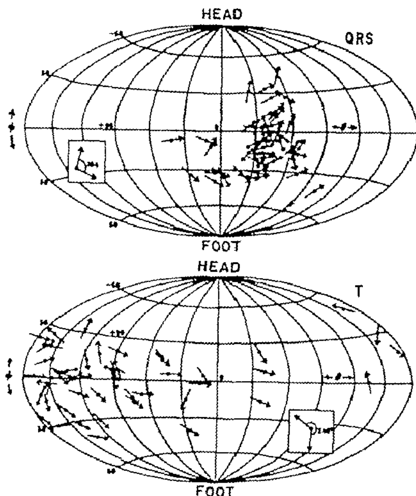


Fig. 2. Axis maps showing individual $\hat{A}_{QRS}$ and $\hat{A}_T$ values (approximate) for patients with left ventricular enlargement. The region within two standard deviations of the mean axes of the normal group is indicated by the stippled areas. The inserts show the range of θ rotations for the normal records. The centers of the maps correspond to a point on the left midaxillary line at the level of the cardiac center.

complexes were recorded simultaneously at paper speeds of 25 and 50 mm. per second. The entire normalization procedure was repeated for the T wave.

As detailed in the previous publication concerning this method, the maximal deflection of the normalized QRS in the X lead is an approximation of the maximal spatial QRS magnitude. The ratio of the peak-to-peak QRS amplitude in normalized leads X and Z is a rough measure of the angular sweep of the heart vector during ventricular excitation and was originally named the "angular sweep index." Since it actually is a measure of the extent to which the heart vector fails to point along a single line, it is more precisely designated and will henceforth be called the "nonlineal index" (see Appendix I). Deviations of the QRS vector from a plane are reflected by the peak-to-peak amplitude of deflections in the normalized Y lead. The ratio of the peak-to-peak deflection in the Y lead to that in the X lead was designated the "nonplanarity index." The area of the spatial QRS loop is approximated by the product of the peak-to-peak amplitude of the QRS complexes in normalized leads X and Z multiplied by $\pi/4$. This area is the magnitude of the polar vector described by Burger.[4] After normalization the polar vector is directed along the negative y axis of the rotated lead system. Its direction prior to normali-

zation can be determined from the rotation angles using a nomograph designed for this purpose. All of these quantitations can be applied to the T wave although the lower amplitude of this deflection makes them less precise The basis for these approximations and some sources of error are discussed in Appendix I

The normalized electrocardiogram yields twelve basic parameters of P which were quantitated these are three angles and three lead voltage amplitudes for the QRS complex, and also for the T wave. In this study the mean $\bar{P}$ of each of these parameters was determined as well as their standard deviation about the mean normal value. If substantial difference in these values between normal and abnormal groups is found it indicates diagnostic utility For example if the mean value for the abnormals differs from the mean normal value then deviations ($P - P_{norm}$) of an individual value of the parameter from the normal mean is likely to be of importance If the mean does not change significantly but if the standard deviation of the abnormal value differs from that of the normals, the absolute value of the deviation of a single measurement from the normal mean $|P - \bar{P}_{norm}|$ is significant

This new parameter here designated q has a normal mean value $\bar{q}_{norm}$ of its own and the deviation ($q - \bar{q}_{norm}$) of an individual measure of it from its normal mean may have clinical value

The map used to display the mean axes of QRS and T was of the standard equal area projection type, also used by Brinberg[4] The map can be considered to represent a sphere centered on the heart center and so oriented that the top of the map corresponds to the part of the sphere near the subject's head and its center to that part of the sphere overlying the left mid axillary line at the same level as the cardiac center The choice of landmarks on the axis map was for the purpose of placing normal axes near the map center

The parameters from normal and abnormal records which were evaluated in this study were compared statistically The statistical methods used are outlined in Appendix II Details of this comparison will be described under results.

Examples of normalized electrocardiograms from the normal and left ventricular enlargement groups are shown in Fig 1 Axis maps showing the distribution of the approximate axes of the $\bar{A}_{QRS}$ and $\bar{A}_T$ vectors are shown in Fig 2 The axes of

*Table I Means and standard deviations of 14 variables considered in this study**

		Normals		Abnormals
		Mean	Standard deviation	Mean
QRS	R (mv)	1 61	0 50	2 38
	X_{pp} (mv)	1 76	0 48	2 46
	Y_{pp} (mv)	0 25	0 01	0 38
	Z_{pp} (mv)	1 31	0 54	1 78
	θ (degrees)	−30 7	25 3	−36 8
	φ (degrees)	18 7	21 5	10 0
	ψ (degrees)	−16 0	20 4	−8 0
T	R_x (mv)	0 47	0 20	0 44
	X_{pp} (mv)	0 47	0 21	0 44
	Y_{pp} (mv)	0 03	0 05	0 04
	Z_{pp} (mv)	0 16	0 07	0 17
	θ (degrees)	46 7	20 2	89 2
	φ (degrees)	25 6	15 3	0 2
	ψ (degrees)	19 2	43 8	6 4

*The symbol R_x refers to the maximum positive deflection in the X lead from the isoelectric line The symbol pp refers [illegible] the peak-to-peak deflection. Standard deviations of the abnormal variables about the normal or abnormal means are not utilized in the analysis given here and are not shown.

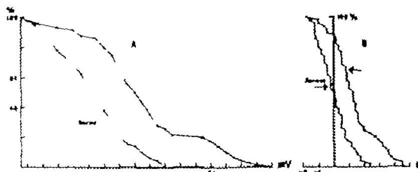


Fig. 3. Per cent of subjects having maximal QRS magnitude (R_{XQ}) deflections larger than the value indicated in abscissa. *A.* Ordinate is millivolts. *B.* Ordinate in standardized form where $= \frac{1}{\sigma}[R_{XQ} - M]$. Here M is the mean of R_{XQ}, and is standard deviation for normals.

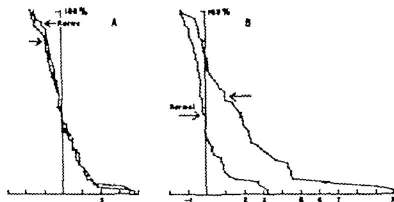


Fig. 4. Standardized distribution curves for (*A*) nonlineal index and (*B*) polar vector magnitude.

$\hat{\lambda}_{QRS}$ from the left ventricular enlargement group were largely located within two standard deviations of the mean $\hat{\lambda}_{QRS}$ axis of the normal group. Eighty per cent of the axes of $\hat{\lambda}_T$ from the enlargement group were located outside two standard deviations of the mean axis of $\hat{\lambda}_T$ for normals. The range of inclination of vectors on the axis maps reflecting the range of the δ rotation for normal records is also shown in Fig. 2. For both QRS and T this range was less than that encountered in records from patients with left ventricular enlargement. Table I shows the means and the standard deviations of the twelve parameters described previously as well as the peak deflections (R_{QX} and R_{TX}) of the QRS and T complexes in the normalized X lead.

A study was made of the utility of employing the indices furnished by the normalized electrocardiogram for the differentiation of normal and left ventricular enlargement records.[8] Fig. 3,*A* illustrates the approach employed. In this figure the values of the maximal QRS magnitude have been plotted to indicate the per cent of records having values above each one shown on the abscissa. Such a distribution curve provides a measure of the reliability of the parameter for the differentiation of normal and abnormal records. For example, in Fig. 3,*A* a level of 1.8 mv. for the maximal QRS magnitude would correctly identify 76 per cent of the left ventricular enlargement records. The same level would falsely identify 32 per cent of normal records as indicating left ventricular enlargement.

In Fig. 3,*B* the above-mentioned results have been plotted in a standardized form in which the mean value of the parameter

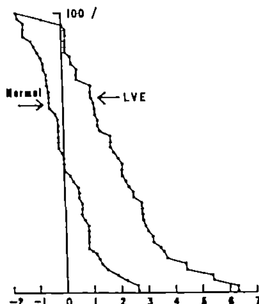


Fig. 5 Distribution curv for standardized form s_c of the distribution of the combined index C = 1.31 s_1 − 0.51 s_3 + 0.88 s_4, where s_1, s_3, s_4 are the standardized variables associated with measurements R_{XQ}, R_{XT} and Z_{PPQ} respectively

for normals has been subtracted from each measurement and the result divided by the standard deviation of the parameters for normals. The use of variables in this standardized form gives a distribution which for normals has a mean value of zero and a standard deviation of one. If the original distribution is skewed, this curve will not intersect the vertical axis at the 50 per cent point. Plotting the distribution curve in this manner makes more evident the differences between normal and abnormal distribution curves.

Fig 4 shows standardized distribution curves for the nonlineal index and the polar vector magnitude. It is clear from Fig 4,*A* that the former is of little use in identifying left ventricular enlargement.

The utility of weighted sums of the individual indices was also evaluated To utilize sums of parameters it was necessary to express each parameter in standardized form. The parameters chosen for this combined index were then added with each value multiplied by the means of the values obtained from patients with left ventricular enlargement. This weighted the final values by an amount proportional to the difference between normal and abnormal mean values. Indices which showed the greatest difference between normal and abnormal mean values were thus given more weight in the final combined index.

A good separation of normal and abnormal groups was obtained by summing in this manner the maximal magnitudes of the normalized QRS and T with the peak to-peak QRS displacement in the Z lead With this combination index (Fig 5) and a separation level of 1 0 correct identification of 74 per cent was achieved with 15 per cent false positive identifications.

Fig 6 shows a distribution plot of a quantity labeled 'T angular displacement index. This index was the sum of the absolute values of the θ and ϕ displacements of the mean T axis from their mean normal values. It is an approximate measure of the great circle distance from the normal mean T axis to the individual T axes.

Since T wave abnormalities are known to be nonspecific, this index was not utilized in the combined parameter shown in Fig 5 even though an improvement in detection of left ventricular enlargement would have been obtained through its use.

Discussion

Two desirable objectives for diagnostic electrocardiography are the reduction of the range of normal variability and quantitative description of the electrocardiogram.

The procedure described as normaliza

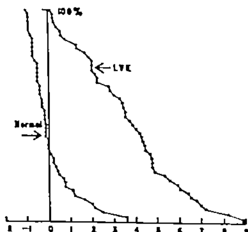


Fig 6. Distribution curv for standardized form s_t of "T" angular displacement index t = $|\theta - \bar{\theta}_{norm}|$ + $|\phi - \bar{\phi}_{norm}|$

tion provides normal electrocardiograms in which the influence of variable cardiac orientation has been reduced. The extent of this reduction is influenced by the validity of the lead system and by the nature of the electrical activity of the heart. If the lead system were perfect and electrical activity in all normal hearts were identical the method would eliminate the influence of cardiac orientation.

The procedure also facilitates quantitative description of electrocardiograms. Certain modifications of the instruments and methods would permit an even more extensive and exact quantitative description of the electrocardiogram. For example, if rotations carried out in the normalization procedure were based on area of deflections, the exact QRS and T mean axes and the ventricular gradient could be obtained from the records.

In this study the method was applied to patients with probable left ventricular enlargement and these records were compared with those of normal subjects. As stated before, the purpose was not to establish new criteria for the diagnosis of left ventricular enlargement but to evaluate the promise of the procedure of normalization as a diagnostic aid. The statistical treatment of results illustrates analyses which become possible when the electrocardiogram has been described in quantitative terms. None of the parameters which were found to be different in normal and left ventricular enlargement records are specifically considered in current electrocardiographic criteria for left ventricular enlargement. It appeared, therefore, that the procedure of normalization showed promise of being useful in the recognition of this lesion. The use of a combination of parameters as an index of the abnormality seemed to have special diagnostic promise.

Definitive demonstration of the diagnostic utility of the normalization procedure will require its application to larger numbers of subjects. The reliability of the method for differentiating various abnormalities requires investigation. Pathologic confirmation of the presence of lesions such as left ventricular enlargement will also be required. Until such studies are made, the results of the present investigation illustrate the application of a quantitative method of electrocardiography and strongly suggest that the method may be useful in the recognition of left ventricular enlargement.

Summary

A new method of electrocardiographic recording and analysis has been applied in a clinical study of left ventricular enlargement. The method consists of effective rotation of an orthogonal lead system to the position at which the leads match a predetermined pattern as closely as possible. The method furnishes approximate values for mean QRS and T axes, maximal magnitude of QRS and T vectors, polar vector magnitude and direction, and of the extent to which the direction of the heart vector deviates from a single direction and from a plane. Modifications of the method to include integration of the electrocardiogram will also furnish the ventricular gradient. Compensation for differences in heart orientation is intrinsic in the method. The parameters evaluated in this study provided various degrees of separation of the normal and abnormal records. The separation was improved by using indices composed of weighted sums of the individual parameters, with weighting factors determined by standard statistical procedures.

Appendix I. Characterizing variations of the heart vector in terms of normalized electrocardiograms

The heart vector can fluctuate in one, two, or three dimensions. If its direction remains constant while its magnitude changes, then the fluctuation will be one dimensional. If its direction changes but some plane exists such that the vector remains within the plane throughout the complex, then its fluctuation is two dimensional. If no such plane exists, then the fluctuation is three dimensional.

The procedure for normalizing electrocardiograms which is used here has the property that the y output will be zero if the fluctuation is two dimensional and both the y and z outputs will be zero if the fluctuation is one dimensional. A normalized record, therefore, reveals at a glance the extent to which the heart

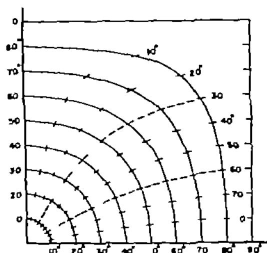


Fig. 7. Nomograph used to determine the direction of the polar vector.

vector tends to point in one direction as well as the planarity of its sweep.

Quantitation of the degree to which the heart vector approximates a unidirectional vector or a planar vector can be achieved in terms of the peak-to-peak amplitudes of the three normalized leads. We may define as a measure of the tridimensionality of the fluctuation the nonplanarity index given by the ratio of the peak-to-peak deflection in the y lead to the peak-to-peak deflection in the x lead. If this index is zero the motion of the heart vector is planar.

In a similar fashion we may define a nonlineal index given by the ratio of the peak-to-peak deflection in the z lead to that in the x lead. If the axis of the heart vector is unchanging, pointing along a fixed line, this index will be zero. We have previously referred to this ratio as the "angular sweep index," but since it is not related in a simple way to the angular excursions of the heart vector, we prefer the new terminology.

If the heart vector loop is elliptical with the isoelectric point at the narrow end, then the nonlineal index is the ratio of the width of the loop to its length. If the isoelectric point is not precisely at the end, the index is somewhat higher than the ratio of the width to the length, but the difference is substantial only with very narrow loops.

A quantity of some interest in electrocardiography is the Burger polar vector

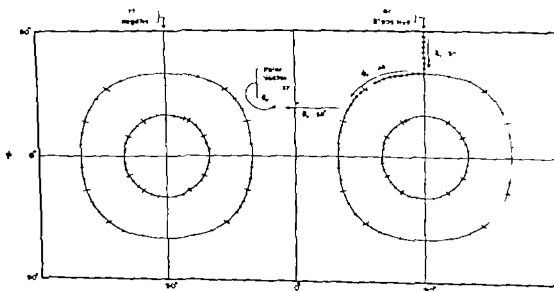


Fig. 8. Determination of the angles θ and ϕ representing the direction of the polar vector from the angles of normalization θ_n, ϕ_n, λ_n. This is achieved by rotating the negative y axis through these angles in reverse order with reverse sense. Arrows on the closed loops indicate the direction of travel when ϕ is positive. (The nomograph in Fig. 7 is used for this rotation.) During the reverse θ rotation the direction of travel is to the left if θ is positive.

$\vec{P}$ If the heart vector loop is planar and elliptical the magnitude $|\vec{P}|$ of Burger's polar vector will be

$$|\vec{P}| = \frac{\pi}{4} (X_{PP}) (Z_{PP})$$

It is implied here that the resolver knob θ is so adjusted after the resolving procedure that the deflection in the z lead is minimum If the isoelectric point is at the end of the loop that setting will result automatically from the usual normalizing procedure but small alterations in the setting may be needed for precision if it is not. Our experience is that the value of the polar vector computed with the formula given above differs only slightly from that obtained with X_{PP} and Z_{PP} from the normalized records without adjustment for minimizing the deflection in the Z leads.

If the heart vector loop is not elliptical the formula given above will be somewhat in error

The normalization procedure orients the plane of the loop so that is is perpendicular to the y axis. Consequently after normalization the polar vector points along this axis. The original direction of the polar vector can be determined by performing on the negative y axis the rotations made by the resolver in opposite sense and reverse order Thus the negative y axis is first rotated about the x axis through an angle $-\theta$ next about the z axis through an angle $-\phi$ and finally about the y axis through an angle $-\theta$ the negative y axis then points in the direction of the polar vector Of considerable use in making the first of these rotations is the nomograph shown in Fig 7 This nomograph represents a map of one octant of the surface of the sphere Fig 8 shows an example of a determination of the direction of the polar vector from the setting of the resolver knobs, using this nomograph

Appendix II. Statistical approach

The statistical problem of making diagnoses from results of laboratory measurements is not complex provided that certain simplifying assumptions are made We assume that the disease is either present or not i.e. there is no question of degree and that n measurements are made on each subject, yielding values v_1 v_2 v It is also assumed that each of the measurements has a Gaussian distribution which has in normals a mean $\bar{v}_{kn}$ and that the effect of disease is to change the means to $\bar{v}_{kd}$, leaving the standard variations σ_1 σ_2 σ of the measurements as before. It is assumed further that the variables are uncorrelated

Under these circumstances given a set of v_k values from an individual subject, the reliability of detection of the disease for a specified rate of false positives, is maximized by using the sum

$$Z = a_1 s_1 + a_2 s_2 + \quad a_n s_n$$

where s is the standardized variable

$$s_k = (v_k - \bar{v}_{kn})/\sigma_k$$

and a_k is the weighting factor

$$a_k = (\bar{v}_{kd} - \bar{v}_{kn})/\sigma_k$$

If Z exceeds some value Z_o, then the disease is assumed to be present The value Z is adjusted to give the desired compromise between false positive rate and reliability of detection of the disease

The variables used in this study had distributions which differed considerably in some cases from the Guassian as well as changes in the standard deviation of the variables between normal and abnormal groups and a certain degree of correlation Nevertheless, a substantial improvement in the reliability of detection for specified false positive rates was achieved with the combined variable Z The use of more elaborate statistical procedures, free from the foregoing assumptions, will undoubtedly provide an even greater reliability of detection. However it is not certain at the moment whether this improvement will be sufficient to justify the increased statistical complexity

The procedure outlined here can be easily extended to deal with many diseases.

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The histologic structure of the pulmonary trunk in patients with primary pulmonary hypertension

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The etiological factors involved in idiopathic or primary pulmonary hypertension (PPH) remain unknown. Recent studies have suggested that in a small proportion of patients with this condition the pulmonary hypertension may have been present from birth, although in most the hypertension of the lesser circulation is acquired later in life. The present report describes the microscopic structure of the elastic tissue in the media of the pulmonary trunk in five patients with proved PPH in an attempt to determine the congenital or acquired basis for this disease.

Material and methods

Five patients who had PPH were studied. Each had severe pulmonary arterial hypertension as determined by cardiac catheterization (Table I), and at autopsy none had congenital cardiac anomalies. All five patients fulfilled the criteria generally accepted for the diagnosis of PPH, i.e., hypertension of the lesser circulation, absence of primary cardiac anomalies, and absence of significant parenchymal disease of the lungs. In sections of the lungs from Patient 5 (Table I), multiple cholesterol granulomata of undetermined etiology were found. These granulomata, however, had no apparent association with the pulmonary arteries and thus were not believed to have played a role in the production of the pulmonary hypertension. At autopsy, all five patients had dilatation of the right ventricle, right atrium, pulmonic valve ring, and pulmonary trunk, hypertrophy of the right ventricle, and atherosclerosis of the pulmonary arteries. The hypertensive pulmonary vascular changes in each of the patients were of Grade 5/6 severity (classification of Heath and Edwards[1]). Four of the five patients were females. The age range was 8 to 29 years.

Transverse blocks of the pulmonary trunk and ascending aorta were removed

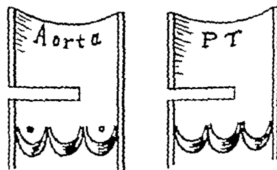


Fig. 1. Diagram of the pulmonary trunk (P.T.) and ascending aorta illustrating the site from which sections for histologic study were obtained.

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from sites 1 cm above the respective semilunar valves (Fig 1) fixed in 10 per cent formalin and embedded in paraffin in the usual way The histologic characteristics of the elastic tissue were studied in both vessels in sections cut 6 micra thick and stained by Van Gieson s method for elastic fibrils. In each instance the tissue of the pulmonary trunk was designated as aortic or adult pulmonary in type (Table I) This classification is based on the studies of Heath and associates.

Results

The aortic or fetal configuration of the elastic fibers of the pulmonary trunk was present in one, and the normal adult pulmonary configuration was present in three of the five patients in this study (Table I) In Patient 4 the configuration was neither adult pulmonary nor aortic in type, but intermediate (transitional) between these two. The aorta was normal in all five patients. Photomicrographs of transverse sections of the media of the pulmonary trunk and ascending aorta in each of the five patients are shown in Figs. 2-6.

Discussion

In the normal newborn infant the pressure in the pulmonary trunk is similar to that in the aorta Shortly thereafter however the pressure in the former falls considerably whereas the pressure in the latter changes slightly Coincident with the changes in the pressure in the lesser circulation after birth a change in the configuration of the elastic tissue in the media of the pulmonary trunk occurs. According to Heath and associates at birth the configuration of the elastic tissue in the pulmonary trunk is similar to that in the ascending aorta (Fig 7) During the first few months of extrauterine life, the elastic fibrils in the pulmonary trunk decrease in number become irregular fragmented shortened and frequently clumped or club shaped By 6 months of age the configuration of the elastic tissue in the pulmonary trunk is distinctly different from that in the aorta and by the end of the second year the adult pulmonary type of elastic configuration of the media is established (Fig 8) The configuration of the elastic tissue in the aorta does not change from birth to adulthood. Its media consists of long uniform tightly packed parallel elastic fibrils. When pulmonary hypertension is acquired later in life as in some patients with atrial septal defect (Fig 9) or rheumatic mitral stenosis (Fig 10) the configuration of the elastic tissue in the pulmonary trunk is unchanged from the normal adult-pulmonary type. On the other hand when pulmonary hyper

Table I Data from five patients with primary pulmonary hypertension

Patient	Age (yr.), race sex	Length of illness from onset of symptoms (yr.)	Cardiac catheterization: Pulmonary arterial pressure (mm. Hg) S/D (M)	Cardiac catheterization: Brachial arterial pressure (mm. Hg)	Cardiac catheterization: Index pulmonary blood flow (L/min./M²)	Type configuration of elastica in media of pulmonary trunk
1 A54-32	29 W F	3	120/40		1 52	Adult-pulmonary
2. A56-160	22, W M	3	88/54 (61)	100/60 (75)	1 30	Adult-pulmonary
3. A57 215	25, W F	2 ½	90/34	96/74		Adult-pulmonary
4. A58-21	8, W F	2	190/100 (130)	90/55 (60)		Transitional
5. A60-219	16, W F	2†	192/5‡	138/90 (123)	2 14	Aortic (fetal)

*S/D (M) Systolic/Diastolic (mean).
†Died during cardiac catheterization procedure.
‡Right ventricular pressure. Pulmonary artery not entered, but pulmonary valve normal at autopsy

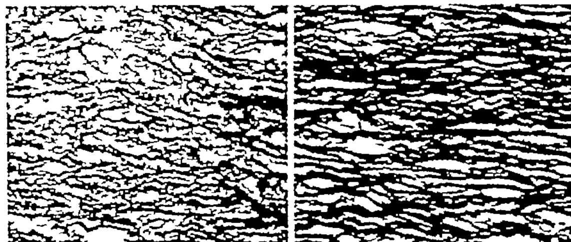


Fig. 2. Case 1. Pulmonary trunk (*left*); ascending aorta (*right*). The configuration of the elastic fibers of the pulmonary trunk resembles that of the adult pulmonary type. Elastic tissue stains ×155.

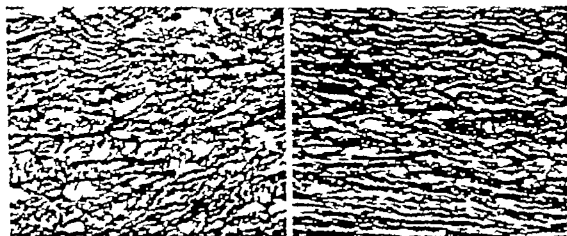


Fig. 3. Case . Pulmonary trunk (*left*); ascending aorta (*right*). The elastic fibers of the pulmonary trunk are of the adult pulmonary type. Elastic tissue stains ×155.

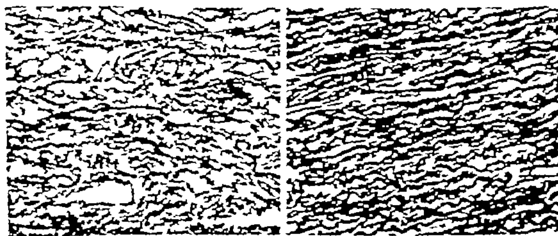


Fig. 4. Case 3. Pulmonary trunk (*left*); ascending aorta (*right*). The elastic fibers of the pulmonary trunk have an adult configuration. Elastic tissue stains ×155.

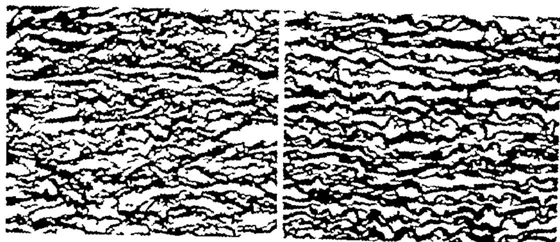


Fig. 5 Case 4. Pulmonary trunk (*left*) ascending aorta (*right*). The configuration of the elastica of the pulmonary trunk is transitional, being neither fetal nor adult-pulmonary in type. Elastic tissue stains ×155

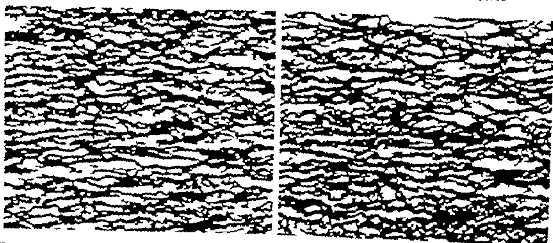


Fig. 6 Case 5. Pulmonary trunk (*left*) ascending aorta (*right*). The configuration of the elastic fibers of the pulmonary trunk is of the fetal type, being indistinguishable from that of the ascending aorta. Elastic tissue stains; ×155.

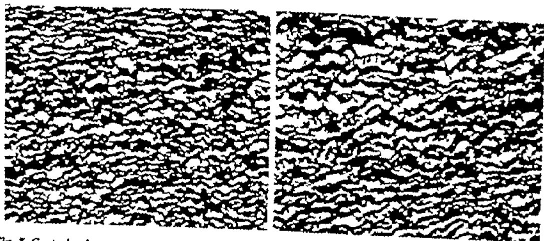


Fig. 7 Control pulmonary trunk (*left*) and ascending aorta (*right*) in 19-hour-old newborn infant. The configuration of the elastic tissue of each is similar. Elastic tissue stains ×133

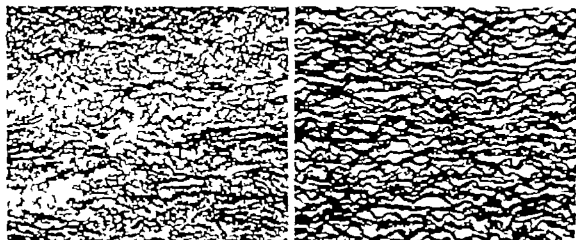


Fig. 8. Control pulmonary trunk (*left*) and ascending aorta (*right*) in a 20-year-old woman. The media of the pulmonary trunk has considerably fewer elastic fibrils than does the media of the ascending aorta. The configuration of the elastica of the pulmonary trunk is of the normal adult pulmonary type. Elastic tissue stains ×135

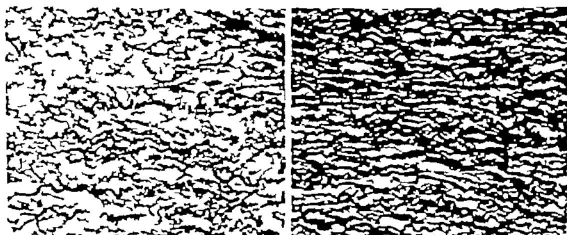


Fig. 9. Pulmonary trunk (*left*) and ascending aorta (*right*) in a 31-year-old woman with atrial septal defect and secondary pulmonary hypertension. The configuration of the elastica of the pulmonary trunk is of the normal adult type, indicating that the hypertension of the lesser circulation was acquired later in life. Elastic tissue stains ×155

tension is present from birth as in patients with large ventricular septal defect (Fig. 11) or widely patent ductus arteriosus, the fetal aortic-like configuration of the elastic tissue in the pulmonary trunk persists.

The presence of the adult pulmonary configuration in three of the five patients with PPH in this study may be interpreted as indicating that pulmonary hypertension was acquired in these cases. The finding of a definite aortic-like, fetal configuration of elastic tissue in one patient in this study suggests that pulmonary hypertension was present from birth in this instance and the transitional configuration in the other patient may be indicative of pulmonary hypertension of milder degree from birth. The results of this study are similar to those reported by Heath and Edwards[1] and by Farrar and associates.[2] The former investigators found an adult pulmonary configuration of the elastica in the pulmonary trunk in five and a transitional configuration in one of six patients with PPH

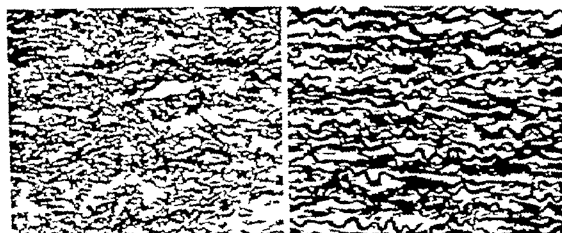


Fig. 10 Pulmonary trunk (*left*) and ascending aorta (*right*) in 32 year-old woman with rheumatic mitral stenosis and secondary pulmonary hypertension. The configuration of media of the pulmonary trunk is of the adult-pulmonary type, indicating that the pressure in the pulmonary arterial circuit was at one time normal and that the hypertension was acquired Elastic tissue stains X155

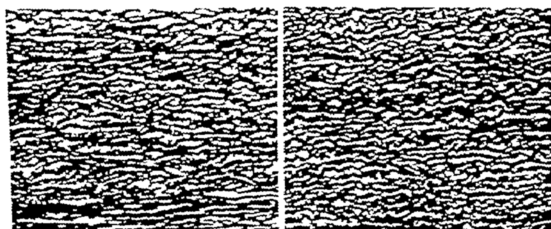


Fig. 11 Pulmonary trunk (*left*) and ascending aorta (*right*) in an 8-year-old boy with large ventricular septal defect and pulmonary hypertension The aortic-like or fetal configuration of the elastica of the pulmonary trunk would indicate that the pulmonary hypertension was present from birth. Elastic tissue stains X155

Farrar and associates found an adult pulmonary configuration of the pulmonary trunk in two and a transitional configuration in one of three patients with PPH studied at autopsy

From the data in Table I it would be impossible to make a definite correlation between the type of configuration of elastic tissue in the pulmonary trunk and the age, length of illness pulmonary arterial pressure or pulmonary blood flow in these patients. The pulmonary arterial pressure however appears to be slightly higher in those patients with the aortic or transitional type of pulmonary trunk. The conclusions of Heath and Edwards[3] would indicate that one (Patient 5 Table I) and possibly two (Patient 4 Table I) of the five patients in this study had pulmonary hypertension for periods of 16 and 8 years respectively

I wish to thank Dr Eugene Braunwald Chief Cardiology Branch National Heart Institute for his helpful suggestions during the preparation of

this manuscript and for his allowing me free use of the cardiac catheterization data. In addition I wish to express my appreciation to Dr. Jesse Edwards, Professor of Pathology, Mayo Foundation and Graduate School, University of Minnesota, for reviewing the histologic sections.

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On the origin of the second heart sound

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In 1832 Rouanet[1] used a model of excised valves to demonstrate that the second heart sound may have its origin in valvular closure. Since that time a wide variety of other mechanisms have been proposed to account for the genesis of the heart sounds.[-4] Although within recent years the valvular origin of the first and second sounds has become generally accepted the actual mechanisms which produce the sounds remain a matter of discussion According to Wakind and Talbot proposed theories still do not account for the build up of pressure and momentum which must precede sound production " We have carried out studies on the production of sound in the left outflow tract and semilunar valves that may account for these requisites of sound production

The semilunar valves and a short section of the aorta were excised from the fresh hearts of steers and dogs. A Lucite cannula was tied into the thoracic aorta so that air could be blown retrograde into the aorta and cause the valves to snap shut. The action of the valves and the resulting sounds were recorded and photographed at 64 frames per second

Consecutive frames of a closing valve are shown in Fig 1 and recorded sounds are shown in Fig 2. Fig 2 demonstrates in sequence the two types of vibration generated (1) continuous vibrations of the valve and walls as fluid passes through the leaflets (as in murmurs) and (2) intense vibrations of short duration associated with valvular closure. When the valves were amputated or were held open by sutures, only the first type of vibration was observed.

Although air rather than liquid was used observation of the preparation showed that during the process of closure the valve leaflets ballooned out from the line of attachment to the wall rolled together with increasing momentum and then closed the corpora arantii were the last points of apposition. Valvular closure vibrations did not appear until the closure was complete. The rolling together of the valves is demonstrated in Fig 1

Since the cusps billow together with increasing momentum, the corpora arantii come into apposition with greater force than do other portions of the coapting leaflets. It is the sudden snapping together of these corpora that provides sufficient energy to vibrate the tensed leaflets, much like a sounding board. Our experiments showed that malfunction of one leaflet reduced the vibration of closure during the apposition of the two unaltered leaflets. This may be related to the fact that the remaining leaflets are not able to attain as great a closing velocity as the cusps in the unaltered valve.

The theory that the vibration is generated by the development of tension in

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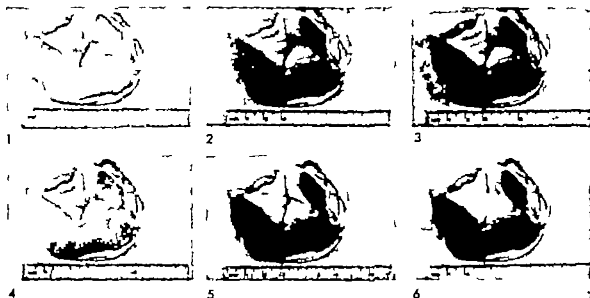


Fig. 1. Progressive closure of aortic valve. 16 mm film at 64 frames per second.

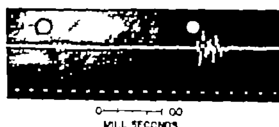


Fig. 2. Oscillographic trace of valve sounds filtered through 600-2,000 cycle per second band-pass filter. 1, Air flow through aortic valve without closure. 2, Valve closure sound.

the leaflets is challenged since the valves are already tensed before the vibration begins. The theory that sound is produced as the valve margins snap together is also not applicable since in the acceleration of the valves away from the walls the valve margins roll—not snap—together. Heart sounds may thus be viewed as having their origin in the tensed valve leaflets, which are caused to vibrate by the sudden whip-like snapping of the ends of the valves after their acceleration away from the walls of the outflow tract.

I wish to acknowledge the stimulation and support of Dr. Simon Rodbard during the course of these studies.

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Pulmonary hypertensive effects of bretylium tosylate in the dog

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Bretylium tosylate is a new hypotensive agent which inhibits the peripheral sympathetic nervous system and has little effect upon the ganglia Since this compound was introduced in 1959 by Boura and his associates,[1] it has been shown to elevate the pulmonary arteriolar resistance of man and the total pulmonary vascular resistance of sheep This report describes the pulmonary vascular effects of this drug in dogs.

Methods

Fifteen fasting mongrel dogs were anesthetized with intravenous pentobarbital (28 mg per kilogram) Cardiac catheters were inserted into the main pulmonary artery pulmonary capillary wedge position and femoral artery The positions of the catheters were verified by fluoroscopy pressures, and autopsy A small polyethylene catheter (PE 50) was placed in the left atrium by transbronchial left atrial puncture. Respiration was maintained by positive pressure and airway pressure was measured by needle puncture of the respirator tubing Pressures were measured by strain-gauge transducers, and mean pressures were obtained by electronic integration Zero level for pressures was one half of the anteroposterior diameter of the thorax in the supine position.

Cardiac output was determined by the indicator-dilution method using indocyanine green. Blood was sampled at a constant speed from the femoral artery through a Gilford densitometer which was calibrated by the pooled-sample method of McNeely and Gravallese Because of electronic malfunction the Fick principle was used to calculate flow in one animal Oxygen content of samples of femoral arterial blood was determined in the Van Slyke manometric apparatus. The pressures and dilution curves were recorded by a direct writing Sanborn oscillograph

Pulmonary blood volume was calculated by the method of Milnor Jose, and McGaff[3,4] and was taken to be the difference between the dilution volumes calculated from rapidly consecutive injections of indicator into the pulmonary artery and left atrium Thirty duplicate measurements of control pulmonary blood volumes in dogs yielded a standard deviation of 10 9 ml. per 10 kg and a standard error of the mean of 2.0 ml per 10 kg [4]

Control observations of pressures flow and volumes were made in duplicate 5 minutes apart Bretylium tosylate† was

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†Kindly furnished as Darenthin by Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N Y

then given intravenously by a slow infusion to 2 animals and as a 2 minute injection to the other 13. The dose was 50 mg. per kilogram in 13 dogs. One animal was given 20 mg. per kilogram and another was given 150 mg. per kilogram. Although these dosages are higher than those used by other investigators, they were used since they yielded the observed effects. Observations were again repeated in duplicate after an average interval of 45 minutes after administration of the drug. Nine paired measurements of pulmonary blood volume were made before and after the injection of bretylium in 6 dogs.

In 4 dogs the spleen was removed before the control observations were made. Three animals were ventilated with 100 per cent oxygen after the effects of bretylium had been studied and all measurements were again repeated in duplicate. Pulmonary vascular resistance was calculated by dividing the difference between mean pulmonary arterial and left atrial pressures by the cardiac output per 10 kilograms of dog and was expressed as resistance units (R.U./10 Kg.). Pulmonary arteriolar resistance was obtained by subtracting mean pulmonary capillary wedge pressure from the mean pulmonary arterial pressure and dividing by the cardiac output per 10 kilograms of dog. Systemic resistance was obtained by dividing mean femoral arterial pressure by the cardiac output per 10 kilograms.

Results

The number of observations and the changes in paired measurements before and after the bretylium are shown in Table I. There was no difference between the results obtained from infusion and those from injection of the bretylium. The cardiac output and pulmonary blood volume did not change significantly. There was a significant decrease in heart rate and a significant increase in hematocrit. In the 4 splenectomized animals the hematocrit

Table I

Parameter	*Number of paired observations*	*Control*	*Bretylium*	*Per cent change*	*Significant change (p value)*
Cardiac output (L./min./10 Kg.)	26	1.428	1.412	−1	
Pulmonary blood volume (ml./10 Kg.)	9	130	155	+19	
Heart rate (beats/min.)	24	169	155	−8	<0.05
Hematocrit (per cent)	17	47	51	+8	<0.05
Oxygen saturation (per cent)	8	94.7	92.7	−2	
Mean pressure (mm. Hg)					
Femoral artery	28	117	140	+19	<0.005
Pulmonary artery	29	11.9	17.0	+43	<0.001
Pulmonary "wedge"	18	5.6	5.3	−5	
Left atrium	27	4.0	3.3	−18	
Airway	3	4.5	4.3	−4	
Resistance (R.U./10 Kg.)					
Pulmonary vascular	26	7.2	13.4	+86	<0.001
Pulmonary arteriolar	16	7.7	13.1	+70	<0.001
Systemic vascular	25	110	154	+40	<0.001

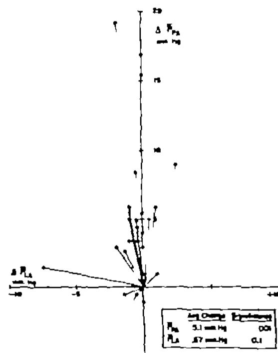


Fig 1 Change in mean pressure in pulmonary artery ($\Delta\bar{P}_{PA}$) and left atrium ($\Delta\bar{P}_{LA}$) after administration of bretylium. The pulmonary arterial mean pressure (ordinate) rose significantly in all but 5 paired observations. Left atrial mean pressure (abscissa) did not change significantly

did not change There was no significant deviation in the arterial oxygen saturation.

The pulmonary (Fig 1) and femoral arterial mean pressures rose significantly but the left atrial (Fig 1) pulmonary capillary and airway pressures did not change predictably Thus, there was a significant elevation in calculated total pulmonary vascular pulmonary arteriolar and systemic vascular resistances. The administration of 100 per cent oxygen had no effect on the bretylium-induced elevation in pulmonary vascular resistance in the 3 animals studied.

Discussion

In man Taylor and Donald demonstrated that bretylium causes a rise in pulmonary arterial pressure and pulmonary arteriolar resistance. Halmagyi and Colebatch[3] described increased total pulmonary vascular resistance in sheep This study extends these observations to the dog and shows the same effects on the pulmonary vasculature. Pulmonary capillary pressure was measured in 2 sheep by Halmagyi and was found to rise after administration of the drug Whether this represented pulmonary venous constriction or a rise in pressure in the left side of the heart is unknown It is clear however that in man and in the dogs reported on here the elevation in pulmonary arterial pressure is the result of increased resistance to blood flow at the level of small vessels, presumably the arterioles. The lack of significant change in pulmonary blood volume is consonant with this hypothesis and against constriction of most of the vascular bed such as may be seen when serotonin elevates pulmonary vascular resistance and reduces the pulmonary blood volume. The possibility exists that constriction of the pulmonary arteries and dilation of the pulmonary veins would decrease and increase pulmonary blood volume respectively and the volume of blood measured by this method would not change This possibility cannot be ascertained by the method used

Gaffney[7] has suggested that bretylium depletes the heart of catecholamines, yet Boura[1] maintains that it has no influence on the catecholamine content of the adrenals or the sympathetic ganglia. It is possible that some of the effects which were observed were due to release of catecholamines into the circulation, as several authors have suggested. The rise in systemic arterial pressure is probably due to the elevated level of catecholamines, and the slowing of the heart rate can be attributed to a reflex vagal effect that results from stimulation of the carotid sinus by the increased pressure. This was not studied in these experiments. The dog's spleen is known to contract with sympathetic stimulation and the rise in hematocrit with the spleen in place and the lack of any change in hematocrit in the splenectomized animals implicates the spleen as the source of this additional red cell mass. It is important to note that the elevated pulmonary resistance was not due alone to increased blood viscosity secondary to the elevated hematocrit for in the splenectomized animals with no change in hematocrit a significant rise in resistance was still found after the bretylium had been given.

The lack of any change in arterial oxygen

saturation or airway pressure is good evidence that the observed changes were not secondary to anoxia or bronchospasm

The exact mechanism whereby bretylium elevates the pulmonary arterial pressure and resistance remains obscure, but it seems to be a localized effect, at arteriolar level and affects man dogs, and possibly sheep. Further observations on other species with more reactive pulmonary vessels will be of interest.

Summary

A sympathetic blocking agent, bretylium tosylate, was given intravenously in large dosage to 15 anesthetized mongrel dogs with closed chests. This drug caused a significant increase in mean pulmonary arterial pressure, total pulmonary vascular resistance and pulmonary arteriolar resistance. Pulmonary blood volume did not change significantly These changes are compatible with constriction of a small segment of the pulmonary vascular bed such as the arterioles.

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Case reports

Angiosarcoma of the heart

Report of a case and review of the literature

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The diagnosis of primary tumors of the heart has been established principally at the time of postmortem examination. However, there are certain findings present in the clinical evaluation of the patient whose case is to be reported which should at least suggest the possibility of a primary tumor of the heart.

Primary tumors of the heart are extremely rare. The incidence of primary tumors of the heart in 4,000 autopsies was 0.0017 per cent. Metastatic tumors of the heart are more common than primary tumors by approximately 16 to 1. One hundred and thirty-four primary sarcomas of the heart had been reported in the literature by 1955, and of these 8 were angiosarcomas.[1] In 1959, 1? cases of angiosarcomas were reviewed. The case of this patient who had an angiosarcoma of the heart and a review of previously reported instances comprise the present report.[4]

Case report

This was the first admission to the Denver Veterans Administration Hospital for a 43-year-old white, married carpenter who was transferred from a private hospital on Nov. 13, 1959, with a diagnosis of recurrent hemopericardium. The patient had been in excellent health until Oct. 7, 1959, at which time he "passed out" at the breakfast table. He had noted productive cough with hemoptysis since early September of 1959 but denied fever or chest pain. He called his family physician and was hospitalized. Chest x-ray films revealed bilateral pulmonary infiltrations consistent with pneumonitis. On the day after admission he went into shock and was maintained on Levophed for approximately 24 hours. The patient improved steadily and remained in the hospital for 10 days. He was discharged on Oct. 17, 1959. Soon after returning home he noted a fullness in the epigastrium which radiated retrosternally. He was admitted to the private hospital, and several days after admission he became cyanotic and extremely dyspneic. An x-ray film at that time revealed a huge cardiac shadow. A pericardial tap produced 400 c.c. of gross blood which did not clot. He was tapped again approximately 4 days later and 650 c.c. of nonclotting blood was removed. He had a third tap approximately 1 week after the second, at which time 900 c.c. of nonclotting blood was removed. The fluid was examined for tumor cells and acid-fast bacilli; both of these examinations gave negative results. The remainder of his laboratory examination was within normal limits, except for a mild anemia (hematocrit of 30 to 40 per cent). The patient was transferred to the Denver Veterans Administration Hospital on Nov. 13, 1959.

Past history. Noncontributory.

Family history. Noncontributory.

Review of systems. The patient had night sweats approximately 3 months prior to admission; otherwise the review of systems was noncontributory.

Physical examination. Blood pressure was 110/80 mm. Hg. The pulse rate was 80, and the temperature

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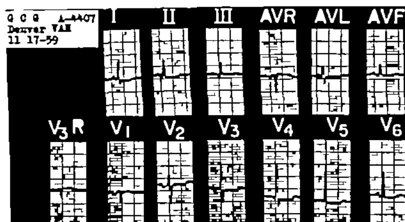


Fig. 1. Electrocardiogram taken on the fifth hospital day showing nonspecific S-T and T wave changes.

was 98.4°F. The respirations were 34 per minute and shallow. The patient was a well-developed, well-nourished white man. He was markedly tachypneic and slightly cyanotic. The pulse was slightly small in volume and normal in quality. A definite paradoxical pulse was present with deep inspiration. The jugular venous pressure was elevated to the mandible when the patient was in the upright position. The ocular fundi showed venous distention. The entire left anterior chest was dull to percussion. There was râles and rhonchi over the base of the left lung. Cardiac dullness extended 4 cm. to the right of the sternum. Palpation of the precordium revealed neither shocks, lifts, nor thrills. The heart sounds were of normal intensity and quality. No murmurs were heard. A faint pericardial friction rub was present. The liver was enlarged 3 fingerbreadths below the right costal margin. Mild peripheral edema was present. The remainder of the examination was noncontributory.

Laboratory examination. The white blood cell count was 28,900, with a differential which showed 59 neutrophiles, 2 lymphocytes, 1 eosinophil, 30 juveniles, 4 myelocytes, and 2 promyelocytes. The hemoglobin was 10 Gm., and the hematocrit was 33. The sedimentation rate was 33 mm. in 1 hour by the Wintrobe method. Prothrombin time was 30 per cent. Repeat examinations were essentially the same. Urinalysis revealed no abnormal findings. The Lee-White clotting time was normal. The total protein was 6.9 Gm. per cent, with 2.6 Gm. per cent albumin. The total bilirubin was 2.8 mg. per cent, with a direct of 1.0 mg. per cent. The serum glutamic oxalacetic transaminase (SGOT) on the first hospital day was 1,800 units, on the fourth hospital day it was 660 units, on the sixth day 100 units, and on the eighth day 72 units. Determinations of SGOT on the succeeding 7 days were normal. Three lupus erythematosus preparations were negative. The bilirubin remained essentially unchanged throughout the hospitalization. An aspiration of bone marrow from the sternum was made and no tumor cells were seen. The bone marrow was compatible with a leukemoid reaction. Six blood cultures were negative. Three pericardial fluid cultures were negative.

Electrocardiogram (Fig. 1). The S-T segments were depressed and the T waves were flat in Standard Leads I, II, V_1, and V_{4-6}. The P waves and QRS complexes were normal.

X-ray examination. A chest x-ray film revealed that the cardiac silhouette was considerably enlarged and had the appearance of left ventricular enlargement (Fig. 2).

Course in hospital. Because of the severe respiratory distress, elevation of the jugular venous pressure, the large heart shadow on x-ray examination, and the paradoxical pulse, a pericardiocentesis was done on the first hospital day with the removal of 500 c.c. of nonclotting dark red blood. Ten cubic centimeters of T 1824 were injected intravenously



Fig. 2. Posteroanterior roentgenogram of the chest taken Nov. 19, 1959 (seventh hospital day), showing greatly increased transverse diameter of the heart with relatively small vascular pedicle.

Table I Summary of pertinent data of all previously reported cases of angiosarcoma of

Author	Age Sex Race	Symptoms	Physical	Lab.	X-ray
Redtenbacher 1889	22 M W	Pain in left chest	Diminished PMI weak pulse, friction rub		
Hewer and Kemp[19] 1936	62 F W	Weakness, malaise night sweats, hemoptysis, radicular pain in thorax	Cardiomegaly distant heart tones		
Gros and Englehardt[19] 1937	45 F W	Spasms of left arm, left hemiplegia	Cardiomegaly BP 110/60, 5 years (M) at apex		
Choisser and Ramsey[14] 1939	26 M W	Weakness, S O B. Pain in left arm, night sweats	Tachypnea, BP 115/90, elevated JVP cardiomegaly no PMI distant tones, cyanosis	NPN 46	Heart enlarged to left. Right pleural effusion
Choisser and Ramsey 1939	30 M W	Weakness S.O B tender RUQ	Tachypnea cyanosis, BP 110/0 cardiomegaly no PMI distant tones, hepatomegaly	WBC 13,000	Mass in pericardial effusion
Glasser and Massey 1950	26 M W	Disorientation, chest pain, tachypnea, anorexia	BP 110/70, cardiomegaly heptomegaly fever	WBC 13 000	Enlarged PA cardiomegaly
Tackett, et al.[16] 1950	45 F C	Weakness, vomiting diarrhea, lethargy anorexia, left anterior chest pain	BP 90/70	NPN 136 WBC 15 950 Bilirubin 2 4	Water-bottle heart with irregular borders
Blanchard and Hethrington, 1952	25 M, W	Precordial pain, cough malaise night sweats	Cyanosis, distant heart sounds, cardiomegaly friction rub febrile		Cardiomegaly
Blanchard and Hethrington, 1952	33 M W	Chest pain	Cardiomegaly		Cardiomegaly
Cheng and Sutton, 1955	45 M C	Substernal pain, dyspnea, hemoptysis	BP 100/80 increased JVP cardiomegaly paradoxical pulse, heptomegaly	NPN 50 WBC 14,600 ESR 0	Cardiomegaly with hairy borders
Grosse-Brockhoff and Schreiber 1955	29 F W	Fever malaise, vomiting, D.O.E., chest pain	Cyanosis, BP 120/80, cardiomegaly distant heart tones. Elevated JVP heptomegaly bilateral pleural effusions	ESR 40 WBC 13,200	Large tumor mass from right mediastinum
Groom,[18] 1956	38, M W	Pain in heart weakness, malaise, D O.E.	Tachypnea, elevated JVP blowing diastolic (M) along lower sternal border heptomegaly		Cardiomegaly ESP on right bilateral effusion

Table I is concluded on pages 249-21

the heart

ECG	Hemopericardium	Duration of illness	Metastases	Primary site	Other
	Yes	4 mo.	Lungs	Pericardium or right atrium	Bilateral hemothorax
	Yes	6 mo.	Lungs, bronchial lymph nodes, mesentery ribs	Right atrium	Benign hemangioma of liver and esophagus
	No	6 mo.	None	Left atrium	RHD with MS, polypoid type intracavitary tumor
	N	8 wk.	Pericardium, mediastinum, pleura, liver	Right atrium	*Right hemothorax, right* ventricle involved, polypoid almost occluding tricuspid valve. Reported as Kaposi sarcoma
	Yes	6 wk.	None	Right atrium	Obstruction of tricuspid valve. Bilateral hemothorax
Nonspecific, T-wave changes suggests RVH with strain	N	4 mo	Lungs	Right atrium	Bilateral hemothorax. Petechiae on chest.
Nonspecific, T-wave changes, low voltage	Yes	4 mo	Lungs	Right atrium	Tumor cell in pericardial fluid. Polypoid projection [illegible] tricuspid valve
	Yes	4 mo.	None	Right atrium	Right hemothorax
Recent inferior infarct	Yes	4 mo.	Bones, lungs, liver	Right atrium	Diagnosis made by bone biopsy. Erosion of sternum by tumor. Bilateral hemothorax
RAD Nonspecific T-wave changes. Low voltage	N	5 mo.	Lungs	Right atrium	Diagnosis made by angiocardiogram. *Left* hemothorax. Cavernous hemangioma of the liver
Sinus tachycardia, nonspecific T wave changes	Yes	15 mo.	None	Right atrium	Bilateral hemothorax. Diagnosis made on PA chest film
Low volt, RAD RVH nonspecific St T changes, old anterior infarct	No	8 mo.	Lungs, liver adrenal, ribs	Right atrium	Right *atrium and ventricle* almost completely replaced by tumor

Table I Summary of pertinent data of all previously reported cases of angiosarcoma of

Author	*Age Sex Race*	*Symptoms*	*Physical*	*Lab.*	*X-ray*
Crenshaw 1959	38 F W	Chest pain, cough, fatigue	Cardiomegaly systolic and diastolic (M) at lower sternal border presystolic mitral (M)		Large tumor from right mediastinum
McNall 1962	43 M W	Chest pain, hemoptysis, fever night sweats, abdominal distention	BP 110/80 cyanosis, tachypnea, elevated JVP cardiomegaly friction rub	WBC 29,000 ESR 33 HCT 33 Bilirubin 2.8 SGOT 1800→660→normal	Pericardial effusion, pleural effusion

during the pericardiocentesis. None of the T 1824 was recovered from the pericardial aspirate. The hematocrit of the pericardial fluid was 45 per cent. On the second hospital day the patient was started on isoniazid PAS, and streptomycin therapy because of low-grade fever hemoptysis, a history of night sweats and possible diagnosis of tuberculous pericarditis. On the sixth hospital day the patient temperature rose to 102°F. He was treated with intravenous K oxide with little effect on his low prothrombin time. Skin tests revealed a positive histoplasmin and an intermediate PPD. During the 2 weeks of hospitalization the patient became gradually more dyspneic. Petechiae were noted on the fifteenth hospital day and they rapidly merged into ecchymoses which were localized to the edematous areas. Complete coagulation studies were done and no abnormalities were demonstrable. On the seventeenth hospital day a firm mass was noted in the left supraclavicular region; a biopsy revealed that this mass was a thrombosed vein. The patient also had several purpuric skin lesions on the forehead. Biopsy of one of these lesions revealed acute necrosis. On the nineteenth hospital day the patient's condition deteriorated. A thoracentesis was performed, and 1,000 c.c. of serosanguineous fluid was removed. At the same time, 680 c.c. of nonclotting blood was aspirated from the pericardium. One hundred cubic centimeters of air was injected into the pericardium. An air-fluid level could be seen and the pericardium appeared to be thickened. On the twentieth hospital day 600 c.c. of serosanguineous fluid was removed from the left side of the chest. The patient was started on steroids and intravenous chloramphenicol. On the twenty-first hospital day the patient suddenly ceased to breathe and did not respond to resuscitative measures.

Postmortem examination. An autopsy was performed immediately after death. The transpericardial diameter was 20.0 cm. A massive shaggy red dish-brown, almost impenetrable thrombus covered the entire epicardium and firmly bound the visceral to the parietal pericardium. A loculated cavity filled with blood was present anteriorly and inferiorly within this mass. The right atrium was prominently dilated (Fig. 3). A 1-by 3-cm. tumor which penetrated the atrial wall was present in the right atrium. The endocardium had a granular appearance and showed a few small adherent thrombi. The heart and adherent blood clot weighed 730 grams, and the heart showed no other intrinsic cardiovascular abnormalities. There was no evidence of ventricular hypertrophy. The left subclavian vein was dilated and occluded by a thrombus which projected down the lumen of the innominate vein and into the lumen of the superior vena cava. The right pleural cavity contained 1,200 c.c. and the left pleural cavity 800 c.c., of bloody fluid. The pleural surfaces of both lungs were marked by multiple small, soft, hemorrhagic-appearing nodules which measured up to 2 cm. in diameter. The right pulmonary artery was occluded by a firm, gray, yellow-red thrombus. The right lung contained typical wedge-shaped areas of infarction.

Microscopic sections of the right atrium revealed scattered degenerating muscle fibers widely replaced by neoplasm (Fig. 4). The tumor in this area showed a variegated pattern, being composed largely of spindly cells, fairly well arranged in a fascicular pattern but almost everywhere containing large meandering channels of angiomatous nature that frequently intercommunicated and occasionally contained erythrocytes. The cells which lined the walls of these channels were an integral part of the tumor and they were frequently many layers thick. Individual cells showed spindle-shaped to round vesicular nuclei, prominent nucleoli, acidophilic cytoplasm, indistinct cellular borders, and moderately frequent mitoses. The myocardium was not involved by the tumor in any area, except the right atrium. Microscopic sections of the lungs revealed multiple small nodules of identical tumors scattered throughout the parenchyma (Fig. 5). Typical areas of infarction which had resulted from arterial thrombi were present in the right lung. The left subclavian vein showed complete occlusion by a proliferating mass of tumor cells which formed cavernous channels filled with blood. Some of the mediastinal lymph nodes revealed small metastatic foci of tumor.

The liver weighed 1,440 grams. There was a nutmeg pattern of the central lobular region. Microscopic section revealed marked dilatation of

the heart—Cont'd

ECG	*Hemopericardium*	*Duration of illness*	*Metastases*	*Primary site*	*Other*
Nonspecific St T wave changes	No	6 mo.	Liver lungs	Right atrium	Diagnosis made by thoracotomy and biopsy
Nonspecific St T wave changes, low voltage	Yes	3 mo.	Lungs	Right atrium	Bilateral hemothorax

the central veins and hepatic sinusoids. There was moderate necrosis of the central area of the hepatic cells, with neutrophilic infiltration.

Review of the literature

Pritchard [1] in 1951 reviewed 134 cases of primary sarcoma of the heart. In these patients the symptoms were usually those of obstruction in the superior vena cava. Hemopericardium was not infrequent although the exact incidence was not given. Bizarre arrhythmias were encountered as was a rapidly changing heart shadow on the x-ray films. The most common presenting complaint in the 14 patients with angiosarcoma of the heart was pain in the chest or left arm: 13 of the 14 patients experienced this sensation. Physical examination of the patients whose cases were reviewed showed that 12 had cardiomegaly, 5 had a narrow pulse pressure, 5 had an increased jugular venous pressure, 5 had cyanosis, and 4 had a pericardial friction rub. Laboratory findings were not helpful. X-ray films showed evidence of cardiac enlargement and pleural effusion in the 11 cases in which they were available. In one patient the diagnosis was suggested by lumpy irregularity of the right cardiac border and in another the diagnosis was suggested by venous angiocardiography.[3] Electrocardiograms were reported in 8 of the 14 cases. They showed nonspecific S-T and T wave changes and or low voltage. The average duration of life after the appearance of symptoms was $5^1/_4$ months, the longest period was 15 months, and the shortest was 5 weeks. The clinical course was one of rapid deterioration characterized by severe congestive heart failure which did not respond to any type of therapy. Four cases were diagnosed as angiosarcoma antemortem: one by the finding of tumor cells in the pericardium, one supposedly by chest x-ray examination, one by biopsy of a metastatic lesion, and one by venous angiocardiography. The site of the primary tumor was in the right atrium in 12 and possibly 13, and in the left atrium in the other case. A summary of the findings in patients with primary angiosarcoma of the heart is presented in Table I.

Discussion

In patients who present with evidence of obstruction in the superior vena cava and or hemopericardium a diagnosis of primary angiosarcoma of the heart should be entertained. The patient whose case is reported here had a primary angiosarcoma of the right atrium. The histologic criteria for this diagnosis are those of Cox and Helwig and Landeen and Farber.[4]

Other causes of hemopericardium are benign idiopathic pericarditis, tuberculous pericarditis, metastatic malignancy of the pericardium, traumatic pericarditis, rupture of the heart, and dissection of the aorta into the pericardium. The above mentioned causes of hemopericardium would appear to be improbable in the present patient for the following reasons: (a) In patients with benign idiopathic tuberculous or granulomatous pericarditis the pericardial aspirate is usually serous or serosanguineous but not grossly bloody. (b) In metastatic malig

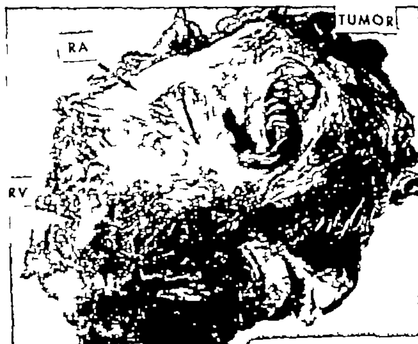


Fig. 3. Gross specimen of the heart, showing tumor mass projecting into the right atrium and the shaggy pericardium.

nancy the pericardial fluid is usually serous or serosanguineous. It can be grossly bloody when the tumor erodes a vascular structure but this is uncommon and occurs late in the clinical course. Usually there is other evidence of metastatic spread.[6] (c) In traumatic hemopericardium there is a history of precordial trauma. The onset of hemopericardium is rapid and usually fatal unless it is relieved immediately. (d) Hemopericardium as a result of rupture of the heart after myocardial infarction usually occurs within the first 14 days after infarction. Survival after rupture of the myocardium or after aortic dissection into the pericardium is exceedingly rare.[7] Blood dyscrasias (i.e., leukemias, hemorrhagic disease, etc.) can result in bloody pericardial fluid; however, there is usually other evidence of the underlying blood disease. Survival of patients with equal pericardial and venous hematocrits for longer than 2 weeks is extremely unusual except in the patients with primary tumors of the heart. In the patient whose case is presented here the recurrent hemopericardium and the 3-month clinical course should have been evidence suggestive of a primary tumor of the heart.

The blood in the pericardium was thought to have stemmed from the tumor itself and not directly from the heart or great vessels. This is supported by (1) the angiomatous nature of the tumor itself (Fig. 4), (2) the relatively slow accumulation of the blood in the pericardial space, (3) a lack of direct communication between the heart and the pericardial space, and (4) failure to recover from the pericardial aspirate the T 1824 which had been injected intravenously.

The marked elevation of the transaminase was considered to be caused by the relatively rapid hepatic congestion and the destruction of liver cells secondary to pericardial tamponade. The amount of myocardial tissue destroyed by the tumor was not believed to be sufficient to cause this elevation. The fall of the SGOT from 1,800 units to normal in 10 days after pericardiocentesis also points to hepatic origin of the abnormality. The persistently low prothrombin time was also thought to be secondary to hepatic congestion, dysfunction, and destruction of cells.[8] The patient's prothrombin time remained in the therapeutic range (15 to 30 per cent) throughout his hospitalization, and this may have contributed to the hemopericardium and/or



Fig. 4. Microscopic section of the primary tumor of the right atrium, showing the multiple cavernous vascular channels: some are filled with red blood cells and lined by bizarre epithelial cells, and some show various stages of mitosis.



Fig. 5. Microscopic section of pulmonary tissue, showing the tumor infiltrating the pulmonary parenchyma.

high hematocrit of the fluid. The lack of response to intravenous K oxide is additional evidence that the SGOT and prothrombin abnormalities were hepatic in origin.

Thickening of the pericardium is thought to be due primarily to infectious processes. In this patient the pericardium was definitely thickened and shaggy and this was due to the formation of thrombus on the

pericardium. Again this finding may be helpful in contributing to the antemortem diagnosis.

The electrocardiographic changes seen in patients with angiosarcoma of the heart are nonspecific. It is interesting to note that in this patient there were only minor S-T segment and T wave changes in the electrocardiogram. There was no diminution of QRS voltage despite the large pericardial effusion (Fig. 1).

The chest x-ray films of this patient also were not particularly helpful in diagnosing the pericardial effusion. The x-ray films presented (Fig. 2) a picture of left ventricular enlargement rather than pericardial effusion.

Striking features of this patient were the recurrent hemopericardium and pericardial tamponade. The steady clinical deterioration resulted in the death of the patient 3 months after the initial symptoms appeared. These findings are the expected ones in patients with a primary tumor of the heart. Table I reveals that 57 per cent of patients with angiosarcoma of the heart had hemopericardium. Ninety-three per cent had a clinical course longer than 2 months. The combination of these two findings should strongly point to the diagnosis of a primary tumor of the heart.

Summary

The case of a patient who had a primary angiosarcoma of the right atrium is reported. Helpful points which may lead to the diagnosis of this condition are: (1) gross blood in the pericardial fluid with the patient surviving more than 2 months, (2) a shaggy, thickened pericardium, (3) no history of trauma, (4) a need for repeated pericardiocentesis, with each one revealing gross blood, and (5) increasing signs of obstruction in the superior vena cava despite pericardiocentesis and lack of evidence of persistent tamponade.

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Cardiopulmonary schistosomiasis

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Infection by the blood fluke *Schistosoma mansoni* may cause gastrointestinal symptoms, and not infrequently hepatic fibrosis with portal hypertension. At times subjects with bilharzial hepatic fibrosis may develop cardiopulmonary manifestations, characterized by pulmonary hypertension, right ventricular hypertrophy, and heart failure. The syndrome, the most severe complication of schistosomiasis, may well be called "schistosomal porto-pulmonary obstruction." The suggested term would indicate the obstructive vascular nature of the disease with involvement of both the portal and pulmonary circuits. It would also imply that the entity is associated with and is a sequela of the increased pressure in the portal circulation which provides collaterals for the direct passage of ova into the lungs.

It is the purpose of this communication to present the salient features of bilharzial cor pulmonale as well as its incidence in the area served by our hospital, which includes 20 towns with a population of 530,000. We believe that cardiopulmonary schistosomiasis should interest not only the physicians in endemic areas, such as ours, but also those on the mainland, since nearly a million Puerto Ricans, with a 10 per cent incidence of schistosomiasis, have become permanent residents there.

Case reports

Case 1. A. J. N. (#87521), a 19-year-old white laborer, was admitted to the hospital because of hepatosplenomegaly which was accidentally discovered during a routine examination in his home town, Guayama, an endemic schistosomiasis area in Puerto Rico. He had had no gastrointestinal symptoms, including bleeding tendencies, nor cardiopulmonary complaints. Physical examination was entirely negative except for hepato-splenomegaly.

Laboratory studies showed a red blood cell count of 2,870,000 with 6.2 Gm. per cent hemoglobin, and a white blood cell count of 3,550 with 67 per cent neutrophils, 25 per cent lymphocytes, 6 per cent eosinophils, and 2 per cent monocytes. The platelet count was 65,000. A rectal biopsy was positive for *Schistosoma mansoni* ova. Liver function tests were normal, except for hyperglobulinemia (albumin, 3.2 Gm. per cent; globulin, 4.8 Gm. per cent), and cephalin-cholesterol flocculation of 4+ in 48 hours. Serum electrophoresis disclosed an increase in the gamma globulin fraction. A chest x-ray film and the electrocardiogram were normal. Esophageal varices were localized in a splenoportogram, which also revealed dilated splenic and portal veins. An aspiration of bone marrow disclosed a hyperplastic marrow with abundance of all marrow elements; the findings were compatible with hypersplenism. Cardiac catheterization studies and pulmonary function tests were normal.

COMMENTS. The classic findings in a patient with bilharzial hepatosplenomegaly are illustrated by this subject. The syndrome usually occurs in young males. The predominant findings are enlarged livers and spleens, and the liver function is generally well preserved, the tests most frequently affected being those which measure abnormal protein func-

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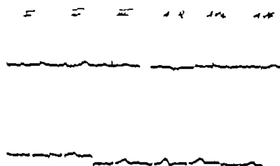


Fig. 1 Case 2 Electrocardiogram recorded before the onset of shortness of breath and interpreted as being within normal limits.



Fig. 2 Case 2 Chest x-ray film showing vascular engorgement and nodular densities in both lung fields more marked in the right attributed in part to schistosomal infiltrates.

tion. The present evidence[4] points to an immunologic mechanism to explain the decrease in serum albumin and the increase in serum gamma globulin. The outstanding complication in these subjects is portal hypertension and its sequela bleeding esophageal varices. However the surgical mortality because of the generally compensated liver function and the youth of the patients, is much lower than that for portal cirrhosis of alcoholic or nutritional origin.

Case 2. M. T. T. (66920), 30-year-old white man, was first admitted to the hospital in June 1957 because of anorexia and abdominal discomfort of 1 year duration. Physical examination showed a well-developed and ill-nourished man in no distress. Blood pressure was 120/80 mm. Hg, pulse was 81 and temperature was 98°F. Pertinent findings were limited to hepatosplenomegaly; the liver was felt 2.5 fingerbreadths beneath the right costal margin, and the spleen extended down to the level of the umbilicus. Laboratory studies showed 3,380,000 red blood cells with 8.99 Gm. per cent hemoglobin and a white blood cell count of 4,000 with a normal differential count. Urinalysis was normal and the blood serology was negative. Examination of the stool and rectal biopsy disclosed the presence of *Schistosoma mansoni* ova; many living as well as dead ova were observed. Liver function tests were normal, except for hyperglobulinemia; the total protein determination was 8.70 Gm. per cent, albumin was 2.95 Gm. per cent, and globulin was 5.75 Gm. per cent. A chest x-ray film was normal; the barium swallow was reported to be negative for varices. An electrocardiogram (Fig. 1) was within normal limits. A liver biopsy revealed focal Schistosoma granulomata with periportal fibrosis. A splenoportogram showed dilated splenic and portal veins, which indicated portal hypertension of intrahepatic origin.

During the subsequent 2 years the patient developed progressive shortness of breath, which necessitated his rehospitalization. At this time besides the previously described hepatosplenomegaly there was evidence of heart failure; the findings were moderate pulmonary congestion, tachycardia, an accentuated pulmonic second sound, tender hepatomegaly and edema of the legs. A chest x-ray film (Fig. 2) disclosed vascular engorgement and small nodular densities, which were best noted in the right lower lung field and were attributed in part to schistosomal infiltrates. The electrocardiogram also showed significant changes from the previous one; the later tracing (Fig. 3) now revealed marked clockwise rotation and right ventricular strain pattern.

The patient was digitalized and was restricted in his use of salt with improvement. Since then he has been readmitted three times for heart failure; the response to therapy has been satisfactory on all occasions. In October 1960 cardiac catheterization was carried out. An increase in both right

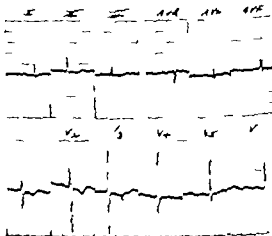


Fig. 3 Case 2. Subsequent electrocardiogram which showed marked clockwise rotation and right ventricular strain pattern.

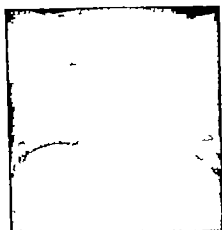


Fig 4 Case 3 Chest x-ray film showing prominent pulmonary conus and right ventricular enlargement.

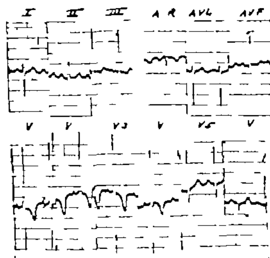


Fig 5 Case 3 Electrocardiogram disclosing right axis deviation and marked right ventricular hypertrophy and strain.

ventricular and pulmonary arterial pressures was found. No significant abnormalities were revealed by oxygen saturation studies, and the pulmonary function tests were normal.

COMMENTS This patient illustrates the progressive development of pulmonary hypertension due to schistosomal pulmonary endarteritis. The pulmonary arterial pressure has not yet attained the levels required for hypertrophy of the right ventricle nor for the marked dilatation of the pulmonary artery segment seen in other subject

Case 3 P D J (82982), 12 year-old white boy was first hospitalized in October 1958, for study of hepatosplenomegaly His symptoms at that time included, besides mass in the left upper quadrant anorexia and frequent episodes of diarrhea. Physical examination showed a poorly developed, pale youngster in no distress. The blood pressure was 100/70 mm. Hg, pulse was 72, and the temperature was 98.6°F The examination was negative except for paleness and marked hepatosplenomegaly Laboratory studies gave the following results red blood cell count of 2,910 000 hemoglobin, 8 3 Gm. per cent white blood cell count, 8,100 with normal differential stools and rectal biopsy positive for *Schistosoma mansoni* ova ; urinalysis, normal. The cephalin-cholesterol flocculation test was 3+ in 48 hours the Bromsulphalein test showed 3 per cent retention in 45 minutes the albumin-globulin ratio was 2.35 to 5 15 Gm per cent the prothrombin time was 19 seconds, with control of 14 seconds. A chest x-ray film was interpreted as being within normal limits, although some prominence of vascular markings was noted.

The patient was discharged to our Spleen Clinic and followed there until September 1959 when he was rehospitalized because of shortness of breath. Apical and pulmonary systolic murmurs were audible at this time, and the pulmonic second sound was markedly accentuated and split. X-ray studies (Fig 4) revealed prominent pulmonary conus and right ventricular enlargement. The right anterior oblique film failed to show any left atrial hypertrophy An electrocardiogram (Fig 5) revealed right axis deviation and marked right ventricular hypertrophy and strain. The splenic pulp pressure was increased to 320 mm. of water and splenoportogram (Fig 6) showed moderately dilated splenic and portal veins with easily visualized varices.

He responded to digitalization and was discharged. In November 1960 cardiac catheterization was performed. A marked increase in right ventricular and pulmonary arterial pressures was encountered. As in the previous case, no abnormalities were revealed by oxygen saturation studies, thus ruling out septal defect The subsequent course was steadily downhill. In January 1961 the patient was readmitted to the hospital in acute heart failure,



Fig 6 Case 3 Splenoportogram showing dilated splenic and portal veins with easily visualized esophageal varices.

Table I. Data obtained in cardiac catheterization

Patient	Age, Sex	Body surface area (square meters)	Pressures (mm. Hg): Brachial artery	Pulmonary artery	Pulmonary artery (Mean)	Right ventricle	Right atrium	Pulmonary wedge
1. A.J.N.	18, M	1.7	110/72	25/15	20	30/5	10/5	9
2. M.T.T.	52, M	1.7	100/50	70/35	50	70/5	7.5/2.5	5
3. P.D.J.	14, M	1.3	108/75	110/70	80	110/50	10/5	8
4.* S.R.	40, M	1.9	110/70	108/56	74	108/10	6/2	9

*Essential pulmonary hypertension.

with marked shortness of breath, engorgement of the cervical veins, moderate pulmonary congestion, tender hepatomegaly, and the complaint of dizzy spells. Oxygen, intravenous digitalis, and mercurial diuretics seemed to improve his condition, but on the fourth hospital day he went into shock and died suddenly. The autopsy disclosed the expected hepatosplenic pulmonary schistosomiasis, with marked dilatation of the pulmonary artery and right ventricular hypertrophy. No congenital or rheumatic heart lesions were found.

COMMENT. An advanced case of bilharzial cor pulmonale has been reported to illustrate the irreversibly malignant course of the disease and the youth of some of the patients. Although the average age of the subjects with the syndrome is usually 30 to 40 years, we observed a 7-year-old girl who died in heart failure. Heavy infection and individual susceptibility seem to be the factors that lead to the rapid development of the disease.

Table I summarizes the hemodynamic findings of cardiac catheterization in 4 of our patients. The data in the first three, who have been reported on above, indicate the usual result in a patient who has bilharzial hepatosplenomegaly but no pulmonary hypertension, and the salient features in those who have a moderate or marked increase in pulmonary arterial pressures. As is apparent from the table, although the mean pulmonary arterial pressure was elevated to 50 mm. Hg in the second patient, the minute cardiac output and the systemic and pulmonary vascular resistances were not significantly altered. On the other hand, in the third case the pulmonary arterial pressure was markedly elevated but the wedge pressure was normal, which indicates a precapillary type of pulmonary hypertension. The cardiac minute output was decreased, whereas the systemic and pulmonary vascular resistances were elevated. In these patients the arterial oxygen saturation is usually unimpaired, or if lowered, not to a degree sufficient to produce cyanosis. Zaky and co-authors[6] recently reported, in Egypt, several cases of bilharzial cor pulmonale with bronchopulmonary shunts which demonstrated a significant increase in oxygen content at different levels in the course of the pulmonary artery. This has not been observed in our patients.

The fourth case included in Table I was one of essential pulmonary hypertension. The patient was a 40-year-old man with hepatosplenic schistosomiasis and bleeding esophageal varices, who also had pulmonary hypertension that was attributed to schistosomal endarteritis. Because of bleeding esophageal varices he underwent emergency surgery for ligation of the varices. He died suddenly 2 days after the operation, and the necropsy showed schistosomiasis of the liver but no pulmonary involvement by the parasite. The classic pathologic lesions of primary pulmonary hypertension, intimal proliferation, and hypertrophy of the media of the arterioles were encountered. Note how similar our catheterization findings in this patient were to those of the patient with schistosomiasis who had advanced pulmonary hypertension.

Discussion

Table II compares the findings of De Faria[7] in 26,000 autopsies performed in the University of São Paulo in Brazil from 1937 to 1952 with ours in the first 1,500 necropsies in the Ponce District Hospital. As is illustrated in the table, we have encountered schistosomiasis more frequently, and the incidence of cor pulmonale has also been relatively higher. On

Oxygen consumption (cc./min.)	Oxygen content (vol. %)				Arterial oxygen saturation (%)	Cardiac output (L./min.)	Resistance (dynes sec. cm.$^{-5}$)	
	Pulmonary artery	Right ventricle	Right atrium	Brachial artery			Total systemic	Pulmonary vascular
205	5 1	5 1	5 1	8 7	93	5 6	1 300	156
180	8 3	8 2	7 9	12 4	90	4 4	1 345	271
161	13 7	13 6	13 7	19 4	89	5 3	2 204	1 725
184	11 9	11 8	11 8	18 1	96	3 0	2 398	1 731

the other hand advanced hepatosplenic bilharziasis has been encountered more often in De Faria's autopsy material. It should be added that these data depict the advanced cases of the disease and in no way indicate the true incidence of these complications that is, portal hypertension and pulmonary hypertension. The generally accepted statistics are that only 5 per cent of patients with schistosomiasis develop the picture of hepatosplenomegaly with portal hypertension and that of these 20 per cent will eventually develop cardiopulmonary manifestations.

As indicated in Table II schistosomiasis was found in 72 patients, either as a primary or incidental finding. Of these 28 had advanced periportal fibrosis with portal hypertension and 18 had pulmonary lesions. In 10 of these 18 subjects the lesions were of such extent as to produce cor pulmonale. 6 of these 10 died in heart failure, 2 from bleeding esophageal varices, 1 of a bleeding peptic ulcer and the other from disseminated cryptococcosis. An additional 7 patients are alive and being followed up. Three of these 7 have had heart failure 1 is showing early evidence of a failing heart, and the other 3 are asymptomatic.

The earliest pulmonary manifestations associated with schistosomiasis occur when the metacercariae are migrating through the lungs—a Löffler syndrome is produced at times. Rarely asthma of allergic origin may occur.

The advanced pulmonary lesions have been classified as parenchymal or vascular. The former are characterized by cough, chest pain, slight hemoptysis, and a radiographic appearance similar to that of military tuberculosis. A case of severe hemoptysis due to erosion of a pulmonary artery by a Schistosoma granuloma was reported previously.

The cardiopulmonary complications de

Table II. Incidence of schistosomiasis in necropsies

	Lopez de Fe so— 24,000 necropsies (1937-1952)	Ponce District Hospital—1,500 necropsies (1956-1961)
Cases of schistosomiasis (primary or secondary finding)	180 (0 7%)	72 (4 8%)
Hepatosplenic bilharziasis	89 (49%)	28 (38 8%)
Cardiopulmonary manifestations	12	10



Fig 7 Section of lung showing an endarteritis and the intimal proliferation of the vessel, as well as giant cell (*indicated by arrow*) surrounding the remnant of *Schistosoma mansoni* ova (×100)

velop as a result of the embolization of the pulmonary arterioles by ova of the parasite. Because all patients with this syndrome have portal hypertension it is generally accepted that the *Schistosoma mansoni* ova *reach the lungs from the portal vein* through the collaterals which are formed with the systemic circulation in an attempt to decompress the portal pressure These ova then provoke an inflammatory reaction within the vessel leading to an endarteritis (Fig 7) and the gradual occlusion of the lumen of the vessel This reaction may push through the wall of the vessel producing a pseudoaneurysm, which consists *of both intra arterial and para-arterial* granulomata. There is also formation of *new blood vessels within the granulomata* the newly formed channels are called *angiomatoids* (Fig 8) These lesions, i.e. the occluded arterioles the pseudoaneurysms, the angiomatoids, as well as others believed to be of allergic origin which consist of necrotizing arteritis with no ova in the involved areas,[9] eventually lead to an increased vascular resistance pulmonary hypertension and cor pulmonale Dilatation of the pulmonary artery secondary *to the pulmonary hypertension* may reach aneurysmal proportions at times (Fig 9)

Clinically the patients are young adults, predominantly of the male sex who complain of shortness of breath oppression in the chest on exertion and pain in the right upper quadrant Edema of the legs occurs in 25 per cent of the patients. On examination *all patients have* hepatosplenomegaly Cardiac auscultation may or may not reveal murmurs, although they are generally present in advanced cases, being usually systolic and heard best in the pulmonary and mitral areas. At times, diastolic murmurs are audible in both *valvular areas and when heard in* the apex, may lead to the diagnosis of rheumatic mitral stenosis. The pulmonic second sound is greatly accentuated and generally split. *Precordial bulging and* a systolic thrust may be present. Clubbing of the fingers is slight when present and cyanosis



Fig 8 Section of lung, showing formation of an angiomatoid. The latter consists of partially obliterated blood vessels with formation of irregular communicating channels that replace the original lumen of the vessel (×100)



Fig 9 Chest x-ray film in case of cardiopulmonary schistosomiasis in which the dilatation of the pulmonary artery attained aneurysmal proportions.

is observed rarely X-ray studies will show enlargement of the right ventricle and dilatation of the pulmonary artery No enlargement of the left atrium will be found thus ruling out mitral stenosis. Angiocardiographic studies are of help in ruling out abnormal cardiac and vascular communications, as well as in confirming the x-ray and fluoroscopic studies. The electrocardiogram shows right axis deviation and right ventricular hypertrophy an incomplete right bundle branch block may be present Hemodynamically the findings include an increase in pulmonary arterial pressure with normal wedge pressure an increase in systemic and pulmonary vascular resistance and a decrease in cardiac output. The arterial oxygen saturation is not significantly impaired the lung function is normal and no shunt is encountered.

Diagnostic difficulty usually arises in distinguishing schistosomal cor pulmonale from rheumatic mitral stenosis and inter atrial septal defects. The presence of an enlarged liver and spleen should suggest schistosomiasis. The absence of left atrial hypertrophy will rule out mitral stenosis whereas the normal oxygen saturation studies in cardiac catheterization and the absence of abnormal cardiac communications by angiocardiograph will eliminate septal defects. The condition which may give identical cardiopulmonary clinical and physiologic findings is primary pulmonary hypertension and as has been shown by the previously described case the presence of hepatosplenomegaly will usually but not always suggest schistosomiasis.

The possibility of precipitating bilharzial cor pulmonale or aggravating pre-existent pulmonary hypertension when portocaval anastamoses are performed for portal hypertension is a distinct hazard This occurs when the bypass operation creates a large and direct communication by means of which the ova gain access to the pulmonary circulation Several patients in our series have developed this complication one of them died in heart failure and two others died of other causes, the cardiopulmonary involvement being a postmortem finding At the present time cardiac catheterizations are being done in patients in whom shunt surgery is planned as well as postoperatively in order to find out whether our clinical impression is a valid one

Summary

1 Pulmonary hypertension and associated hepatosplenomegaly in a patient from an area in which schistosomiasis is endemic should suggest cardiopulmonary schistosomiasis. The clinical and pathophysiologic features of the disease have been presented.

2 Bilharzial cor pulmonale is not so rare as was previously believed and its incidence should increase with our awareness of it as well as with the control of portal hypertension by shunt surgery

3 Although the syndrome is associated with an irreversibly fatal outcome the course may not be so rapidly downhill as has been reported by others. This has been illustrated by two of our case reports.

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Clinical pathologic conference

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Clinical abstract

DR. HEATH A 40-year-old man was admitted to the hospital on April 5, 1951 He had been apparently well until 10 weeks before admission, when he had noticed the gradual onset of swelling of the ankles, loss of energy increasing pallor and breathlessness on moderate exertion.

Three weeks after the onset of these symptoms he developed a rash which he called red spots. He first saw these on his feet and underneath the strap of his wrist watch. Later the spots became generalized in distribution. There was frequency of micturition. His appetite became poor and he lost 14 pounds in weight H had no cough.

The only relevant past history was that he had had scarlet fever when he was 12 years old. There was no history of rheumatic fever

On examination he was pale and thin, and had multiple small skin lesions, as described above. He had pitting edema around the ankles and over the sacrum. Ascites was present. H had slight clubbing of the fingers. There was no distention of the neck veins, and there were no signs referable to the lungs.

The radial pulse was regular at 100 per minute and the systemic blood pressure was 120/70 mm. Hg The apex beat was not palpable. There was systolic murmur over the precordium which was maximal in the third and fourth intercostal spaces immediately to the left of the sternum. The tip of the spleen appeared to be just palpable, but was not felt after May 20.

Hospital course There were occasional spikes of pyrexia up to about 100°F F rther crops of red spots appeared on the body during the whole of the illness. He developed attack of abdominal pain with diarrhea. I spit of these symptoms his condition gradually improved under treatment, and his edema disappeared. However during the latter part of his stay there were several brief episodes of chest pain with increased dyspnea. H was discharged from the hospital on June 26.

An x-ray film of his chest on May 6, showed enlargement of the heart. I addition there were shadows in the left mid zone of the lungs, and there were few small circular shadows at the right base. Three weeks later on May 27 the shadows in the right lung appeared to be smaller and that on the left had become sharply defined.

Readmission to hospital He was readmitted 3 weeks later on July 14 He had remained apyrexial, but with occasional new spots on his body H began to feel ill once more. This time he had an irritant nonproductive cough. He volunteered the information that he had developed sudden pain in the chest. There was no hemoptysis.

Examination on readmission H was very pale and orthopneic. The skin rash and edema had reappeared. The signs referable to the cardiovascular system were the same as those on the previous admission, with the addition of marked distention and systolic pulsation of the neck veins. The liver was now palpable but pulsation was not noted. There were also definite signs in the chest. He had bronchial breathing over the right lower lobe. An x-ray film of his chest on July 28 showed shadowing of the right lower lobe.

Shortly after readmission he developed focal epilepsy which started in the right hand. H then had generalized convulsions, became disorientated and died.

Discussion

DR. DAVISON The history of the onset of an insidious illness with pallor breathlessness and the development of edema of the ankles with ascites is suggestive of nephritis. Cardiac failure is unlikely since there is no history of venous engorgement. Hepatitis is another less likely possibility An examination of the urine would be helpful in the differential diagnosis here. We are given the additional important information that this patient had crops of "red spots" which appeared at sites exposed to local pressure and in places, such as the feet in which there is capillary stasis. These lesions are probably petechiae which are not a common manifestation of nephritis or hepatitis. Since we know he also had fever clubbing of the fingers and a palpable spleen together with a cardiac murmur

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On examination he was pale and thin, and had multiple small skin lesions, as described above. He had pitting edema around the ankles and over the sacrum. Ascites was present. He had slight clubbing of the fingers. There was no distention of the neck veins, and there were no signs referable to the lungs.

The radial pulse was regular at 100 per minute, and the systemic blood pressure was 120/70 mm. Hg. The apex beat was not palpable. There was a systolic murmur over the precordium which was maximal in the third and fourth intercostal spaces immediately to the left of the sternum. The tip of the spleen appeared to be just palpable, but was not felt after May 20.

Hospital course. There were occasional spikes of pyrexia up to about 100°F. Further crops of red spots appeared on the body during the whole of the illness. He developed an attack of abdominal pain with diarrhea. In spite of these symptoms his condition gradually improved under treatment, and his edema disappeared. However, during the latter part of his stay there were several brief episodes of chest pain with increased dyspnea. He was discharged from the hospital on June 26.

An x-ray film of his chest on May 6, showed enlargement of the heart. In addition there were shadows in the left mid zone of the lungs, and there were a few small circular shadows at the right base. Three weeks later, on May 27, the shadows in the right lung appeared to be smaller and that on the left had become sharply defined.

Readmission to hospital. He was readmitted 3 weeks later on July 14. He had remained pyrexial but with occasional new spots on his body. He began to feel ill once more. This time he had an irritant nonproductive cough. He volunteered the information that he had developed a sudden pain in the chest. There was no hemoptysis.

Examination on readmission. He was very pale and orthopneic. The skin rash and edema had reappeared. The signs referable to the cardiovascular system were the same as those on the previous admission, with the addition of marked distention and systolic pulsation of the neck veins. The liver was now palpable but pulsation was not noted. There were also definite signs in the chest. He had bronchial breathing over the right lower lobe. An x-ray film of his chest on July 28 showed shadowing of the right lower lobe.

Shortly after readmission he developed focal epilepsy which started in the right hand. He then had generalized convulsions, became disorientated, and died.

Discussion

DR. DAVISON: The history of the onset of an insidious illness with pallor, breathlessness, and the development of edema of the ankles with ascites is suggestive of nephritis. Cardiac failure is unlikely since there is no history of venous engorgement. Hepatitis is another less likely possibility. An examination of the urine would be helpful in the differential diagnosis here. We are given the additional important information that this patient had crops of "red spots" which appeared at sites exposed to local pressure and in places, such as the feet, in which there is capillary stasis. These lesions are probably petechiae, which are not a common manifestation of nephritis or hepatitis. Since we know he also had fever, clubbing of the fingers, and a palpable spleen, together with a cardiac murmur

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and apparent renal edema we can deduce that the probable diagnosis is one of subacute bacterial endocarditis associated with glomerulonephritis Certainly the later course of his illness is compatible with this. As for the underlying heart lesion we are told that he had a precordial systolic murmur and I take it that this was of sufficient intensity to indicate its origin in organic disease We are not told whether this murmur was of ejection or pansystolic type but it was maximal in the third and fourth left intercostal spaces. From this description I should think it likely that the underlying heart lesion was either a ventricular septal defect or tricuspid incompetence Since no systolic pulsation was reported to have been seen I should think that the former congenital disease was the more likely Of course he may have been suffering from one of the collagenoses, such as disseminated lupus erythematosus or polyarteritis nodosa These diseases are sometimes difficult to differentiate from the conditions that I have mentioned previously but I see no real reason to invoke their presence in this case But I thought that I had to include them for if you do not mention this possibility at any polite medical meeting these days you are not one of the boys." May I have the results of examination of the urine?

DR. HEATH The specific gravity of the urine was 1 012 and proteinuria was present. There were deposits of red cells, and hyaline and granular casts were present. His blood urea on admission was 165 mg per cent and had risen to 210 mg per cent by April 21

DR. DAVISON These findings indicate an active glomerulonephritis. What were the results of the examination of the blood?

DR. HEATH The initial erythrocyte sedimentation rate on April 8 was 107 mm and this gradually fell to 78 mm. by July 21 The white cell count was 5,200 per cubic millimeter on April 8 and this rose to 11 000 per cubic millimeter on July 21 87 per cent of the white cells being neutrophil polymorphs. The hemoglobin level was 46 per cent on April 8 and on treatment this rose to 58 per cent on July 21

DR. DAVISON Well, he has a significant anemia and a severely elevated erythrocyte sedimentation rate. These findings are compatible with both nephritis and subacute bacterial endocarditis Was a blood culture carried out.

DR. HEATH Yes. *Streptococcus viridans* was cultured on April 29 from blood incubated for 72 hours. The bacteria were sensitive to penicillin

DR. DAVISON This is of course diagnostic of subacute bacterial endocarditis. Having established this let us consider the underlying heart lesion. Let us see the roentgenogram of the chest (Fig 1)

The heart is not enlarged and the silhouette is normal. This certainly does not suggest the presence of tricuspid incompetence Furthermore there is no enlargement of the pulmonary arteries, such as would be expected with an elevated pulmonary arterial pressure. I should have thought that a ventricular septal defect without pulmonary hypertension would be most compatible with these radiographic features. I am more interested in the abnormalities that I see in the lung fields. There is evidence of pulmonary venous engorgement as evidenced by the very prominent hilar shadows. The discrete shadows at the bases suggest pulmonary infarcts. I must confess that I am overwhelmed by the size of this roentgenogram when projected onto the screen. It is rather like coming to see Cinemascope and sitting in the front row! I should like to see the acutal films on a viewing box. I take it that he was given massive dosage of penicillin.

DR HEATH Yes, you are right in that assumption.

DR DAVISON I notice that his hemoglobin level rose and that his erythrocyte sedimentation rate fell but it is clear that all was not well because he developed additional symptoms referable to the lungs—and here we come back to the shadows on the chest film. The attacks of breathlessness and chest pain that he had are suggestive of pulmonary embolism. This would fit in well with our diagnosis of ventricular septal defect. because in this disease the vegetations of a superimposed endocarditis occur in the area of the jet lesion on the right ventricle. This is where the left-to-right shunt through the defect impinges on the ventricular wall. Fragments of these vegetations might break off and give rise to pulmonary emboli.

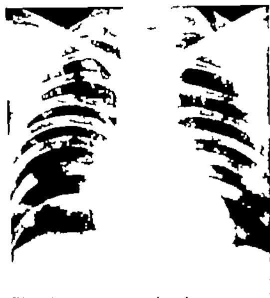


Fig. 1 Chest roentgenogram t the time the patient was admitted t the hospital.

You will note that I have been talking for 23 minutes and I have not yet mentioned electrocardiography I think you ought to congratulate me on my reserve. Let us see it as a matter of course. (The electrocardiograms were shown at this point.) Well, the first ECG is normal and would be compatible with a ventricular septal defect of maladie de Roger" type. The ECG taken 2 months later shows right bundle branch block, ventricular extrasystoles and a picture of right heart "strain if I may be permitted to use that word. This may possibly ndicate progressive pulmonary vascular occlusion

I think that this would explain his deterioration before and after his second admission to the hospital. The systolic pulsation in his neck veins on readmission indicates tricuspid incompetence probably secondary to pulmonary hypertension and right ventricular dilatation. It seems very likely that he had progressive obl teration of the pulmonary vascular bed by embolization.

DR. HEATH You will be interested to know that there was n fact no radiologic evidence of enlargement of th pulmonary arteries or of the right ventricle. However the radiologists were impre ed by progressive increase in size of the shadow of the left hilum. Furthermore this hilar shadow was pulsatile The shadow of the right hilum did not increase in size. What do you think of these findings

DR. DAVISON Increased hilar shadowing usually implies pulmonary venous engorgement secondary to heart failure, consequent upon long drawn out endocarditis. About 40 per cent of the patients with subacute bacterial endocarditis go into cardiac failure probably as a result of progressive valvular damage. The valve orifices dilate and become incompetent. In the case of a ventricular septal defect there is no such mechanism to explain myocardial failure Pulmonary venous engorgement usually gives rise to bilateral increase in hilar shadowing but in the present case we have to account for a difference in size and pulsation between the two hila I think that there are two possible explanations for this. He may have a mycotic aneurysm of the left main pulmonary artery due to impaction of an infected embolus in this vessel On the other hand he may have total aseptic occlusion of the right main pulmonary artery with most of the blood passing to the left lung Of the two I favor the former diagnosis.

To conclude then I think that this patient has a small ventricular septal defect with subacute bacterial endocarditis and associated glomerulonephritis. As a result of recurrent pulmonary embolism he developed pulmonary arterial occlusion and congestive cardiac failure. A large embolus to the left main pulmonary artery led to a mycotic aneurysm. Another led to a fatal cerebral embolism

MR. BURMAN I am struck by the paucity of clinical and radiologic signs of obliteration of the pulmonary vascular bed in view of the fact that you seem con inced that such occlusion occurred

DR. DAVISON We have not been gi en sufficient clinical details to be ure about this. For instance we do not know about the loudness or degree of spl tting of the second sound in the pulmonary area. Furthermore it is very difficult to detect pulmonary hypertension clinically in some patients. However there was certainly evidence of congestive cardiac failure and electrocardiographic evidence of right ventricular strain.

MR. ALLISON Is it not true to say that



Fig 2 Heart opened to show cavity of left ventricle with ventricular septal defect of maladie de Roger type (rrow)

you can have large numbers of small pulmonary emboli without any evidence of infarction so that there might be little in the way of clinical and radiologic evidence of such embolism?

DR. DAVISON Absolutely true. It may be that such pulmonary embolism had occurred throughout the entire course of the illness, and that the effects were noted only in the final stages.

MISS STARKEY What do you think was the mode of production of the purpura in this case?

DR. DAVISON I think it likely that increased capillary fragility rather than embolism was the main cause of the crops of petechiae in the early stage of this man's illness, which I take to be due to acute glomerulonephritis.

MR. BEEHEEJAUN What do you think of the nature of the ventricular septal defect?

DR. DAVISON I think it was congenital

DR. HEATH Having heard Dr Davison's summary of the case, would Dr Davis now tell us what he found at autopsy

DR. DAVIS I carried out the autopsy which was upon the body of an emaciated very pale man who looked considerably older than his age of 40 years. He had edema of the dependent parts, and widespread purpura severe in places, and there were scattered ecchymoses. He had clubbing of the fingernails.

The essential lesion in the heart was as described by Dr Davison a ventricular septal defect. The hole was small and was in the membranous portion of the interventricular septum (Fig 2) There was marked endocardial fibrous thickening around the defect but there were no bacterial vegetations on the left ventricular side. The mitral and aortic valves showed no evidence of rheumatic heart disease. As seen from the right ventricle (Fig 3) there were bacterial vegetations around the septal defect and these had spread onto the tricuspid valve, where there was some destruction of the valve leaflets and also of some of the chordae tendineae. The chambers of the right side of the heart and the tricuspid valve ring were dilated. The heart as a whole was only slightly enlarged it weighed 360 grams. The right ventricular wall was about the upper limit of normal in thickness, about 3 mm

A section of a tricuspid valve leaflet showed the cusp to be surrounded by masses of bacterial vegetations, made up of colonies of bacteria bound together with masses of fibrin and platelets.

With regard to the rest of the body there were the usual changes of congestive cardiac failure—ascites, pleural effusions chronic venous congestion of the liver and



Fig 3 Heart opened to show cavities of the right side of the heart with bacterial endocarditis of the tricuspid valve. The vegetations are indicated by the arrow

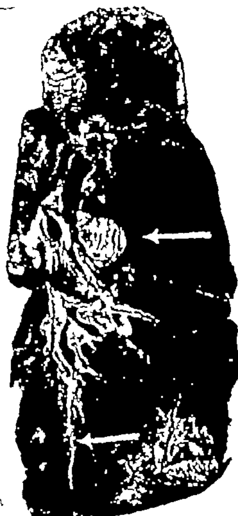


Fig. 4. Left lung sectioned to show mycotic aneurysm of the main pulmonary artery filled with laminated thrombus (*upper arrow*). Septic infarcts are shown by lower arrow.

spleen and so on. The spleen weighed 500 grams, and contained one small *old* infarct. There were no recent infarcts.

The kidneys were slightly swollen; they weighed 330 grams. They were pale in color and on the cut surfaces the normal markings were blurred. In the cortex were numerous small petechial hemorrhages, having the "flea bitten" appearance of focal embolic nephritis. A section showed the typical histologic appearances of this condition with clumps of organisms impacted in many glomeruli with the clumps surrounded by red blood cells filling the space within Bowman's capsules, and with additional red cells present in the corresponding convoluted tubules. There were no macroscopic infarcts in the kidneys. There was no histologic evidence remaining of the acute glomerulonephritis which must have been present during the time of the patient's first hospital admission. This is one of the possible renal complications of bacterial endocarditis, the others being those already mentioned, focal embolic nephritis and multiple macroscopic infarcts which we would expect in cases of bacterial endocarditis of the left side of the heart only.

His death followed epileptic convulsions, and he had a septic infarct which measured about 5 mm. in diameter situated in the cerebral cortex of the pars posterior of the left inferior frontal gyrus just hidden within the Sylvian fissure. A number of small localized hemorrhages were present scattered over the surface of the brain in the subarachnoid space, especially around the left middle cerebral artery and its main branches.

Some of the most interesting features in this case were to be found in the lungs, which were congested and edematous with numerous large hemorrhagic infarcts of varying age, some of which were breaking down to form abscesses. Some were very old and fully organized. Numerous large branches of the pulmonary artery were



Fig. 5. Photomicrograph of edge of mycotic aneurysm, showing two divisions of the pulmonary artery plugged with septic embolus. The branch of the media in the upper division is indicated by the arrows. (Lawson modification of the Weigert-Sheridan method for elastic tissue; magnification ×8.5.)

plugged with large pieces of embolic bacterial vegetations. A mycotic aneurysm which measured approximately 2 5 cm in diameter and which was filled with pale laminated thrombus was present close to the hilum in the left main pulmonary artery within the lung (Fig 4)

Histologically the lungs were congested with dilatation of the capillaries and edema coagulum with iron pigment-laden macrophages in the alveolar spaces. The small pulmonary arteries did not show any evidence of hypertensive pulmonary vascular disease. This was not surprising since the septal defect was small producing the clinical picture of maladie de Roger Sections of the left main pulmonary artery showed the lumen plugged with a mass of infected blood clot containing many colonies of bacteria The media was breached resulting in the development of the aneurysm (Fig 5) Perhaps I might add a point here about the radiologic appearances. The radiologists confidently diagnosed this mycotic aneurysm before death and were so pleased in so doing that they actually came down to the postmortem room to see the autopsy!

The pathologic findings in this case were in agreement with Dr Davison s summary of the case with the important exception that I should consider that the tricuspid incompetence that developed was organic, the result of destruction of the valve leaflets from bacterial endocarditis rather than functional due to increased pulmonary vascular resistance due to the emboli producing right ventricular dilatation

I might also add at this point that I think the petechiae in this case were produced by a combination of two factors—toxic capillary damage and small microscopic infarcts. Organisms have been cultured from purpuric hemorrhages of this type The pulmonary capillary bed is a very coarse filter for organisms as small as bacteria.

DR. EVANS Were there any dental caries or dental extractions prior to his illness?

DR. DAVIS His teeth were quite good and there was no history of dental extraction.

DR. HARRIS Was the damage to the pulmonary artery wall which resulted in the mycotic aneurysm due to embolization of the vasa vasorum?

DR. DAVIS I do not believe that it is necessary to think only of embolization of the vasa vasorum in the causation of the mycotic aneurysm The lumen of the main artery was filled with septic embolus, which led to septic arteritis, and direct damage to the arterial wall Once the elastic tissue and muscle had been sufficiently destroyed the wall would stretch and lead to the formation of an aneurysm

Mycotic aneurysms are not often seen and then usually in the cerebral vessels in cases of bacterial endocarditis of the left side of the heart. The few cases of mycotic aneurysm of the pulmonary artery which have been described have almost all been due to this particular condition we have seen here.

DR. HEATH Perhaps I should add that most intrapulmonary aneurysms are mycotic and secondary to bacterial endocarditis. This is in contrast to aneurysms of pulmonary arteries outside the lungs, which are usually due to pulmonary hypertension with associated cystic medial necrosis. Very rarely these extrapulmonary aneurysms may be congenital or syphilitic.

DR. DAVISON I think that the increased pulsation at the lung hila during the patient s second admission to the hospital was not due entirely to one mycotic aneurysm Substantial obliteration of the pulmonary bed appears to have been an additional factor I think that it is very difficult to decide how much obliteration of the pulmonary bed has taken place, as seen at autopsy unless the vessels are injected.

DR. HEATH Would you agree that, if there was pulmonary vascular obliteration the degree of pulmonary hypertension it produced must have been very slight, for the right ventricle was only 3 mm. thick and the small pulmonary arteries were thin walled?

DR. DAVISON Well of course, I do not really know how much pulmonary hypertension there was—it was not measured—but it seems likely that the right ventricle did not have much chance to hypertrophy and it went into gross failure.

Diagnoses Ventricular septal defect subacute bacterial endocarditis mycotic aneurysm of left main pulmonary artery

Fundamentals of clinical cardiology

Heart failure in hypertensive patients

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It has long been accepted that heart failure is a common complication and a major cause of death in patients with high blood pressure. Thus the mortality from this cause has been variously recorded between 43 and 55 per cent of hypertensive patients,[1-4] with no significant reduction in the mortality rate between 1928 and 1941

Experience in a clinic for the investigation treatment, and follow up of patients with high blood pressure, over a period of 7 years suggested that although hypertension may increase greatly the work of the heart, the heart does not fail unless it is exposed to some additional embarrassment. It is possible that this impression was accentuated by the capacity of hypotensive drugs to reduce the hypertensive work load of the heart and thereby increase the relative importance of these additional factors.

It is the purpose of this paper to assess the cause or causes, o er and above hypertensive overwork of the left ventricle that bring about failure in this common malady

Material

The case histories were examined for all patients admitted to the medical wards of Charing Cross Hospital over the period 1946-1959 and to The Roy l West Sussex Hospital during 1961 A total of 456 hypertensive patients were admitted in heart failure Of these 11 d ed with a few ho rs of admission and have been excluded from the series, since they could not be accurately assessed with regard to history blood pressure and electrocardiography The case histories of the other 445 patients, comprising 247 men and 198 women were reviewed critically from the standpoint of the manner in which their heart failure developed

Criteria

High blood pressure Difficulty is encountered when an attempt is made to define high blood pressure. There is no agreement upon a level of pressure above which a patient may be considered to ha e hypertension In this respect attention has been drawn to the progressive increase in systolic blood pressure found normally with advancing years t is l kely that man patients with so-called essential hypertension ma not in fact ha e pathologically elevated blood pressures, since their level of pressure fall within the upper limit of normality on the distribut on curve

Since it is generally agreed that a high diastolic pressure is of greater significance than a high systolic pressure onl those patients with a diastolic pressure of 90 mm Hg or more were accepted In most the systolic pressure exceeded 180 mm Hg Those with systolic pressures between 150 and 180 mm Hg were included when their associated diastolic pressure was 110

The diastolic pressure was not assessed

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Table I Causes of heart failure in patients with high blood pressure

Cause of heart failure	Number of patients	Average age (yr.)	Died	Average age at death (yr.)	Mortality (%)
Combined cardiac and renal lesions	36	—	15	—	42
Renal lesions	30	—	12	—	40
Malignant hypertension	38	—	17	—	45
Total number of renal cases	104	53.7	44	53.2	42
Cardiac ischemia	223	61.6	44	65.8	20
Valvular lesions	48	—	10	—	21
Respiratory infections	27	—	8	—	30
Miscellaneous	31	—	8	—	26
Total number of nonrenal cases	329	62	70	66.4	24
No cause found	12	—	—	—	—
Total	445	60	114	61.3	26

Mortality rate for renal cases: men 44.4 per cent, women 41.9 per cent.
Mortality rate for nonrenal cases: men 22.3 per cent, women 20 per cent.

while a patient was in acute left ventricular failure since wide fluctuations, particularly elevation, of the level of blood pressure occur during such episodes. In some instances the blood pressure was known prior to the onset of failure; in most, the accepted level of pressure was that noted after failure had subsided and usually just before the patient was discharged from the hospital. Of the 10 patients who died and in whom congestive heart failure had persisted, the average pressure after they were hospitalized was considered to reflect their usual blood pressure.

Heart failure. Patients with evidence of failure of either ventricle were included. For the purposes of analysis, patients were separated into three groups: (1) those with acute left ventricular failure, i.e., attacks of paroxysmal dyspnea or of acute pulmonary edema; (2) patients in congestive heart failure with jugular venous and hepatic congestion and sometimes dependent edema; and (3) patients with both congestive and left ventricular failure.

Ischemic heart disease. A diagnosis of ischemic heart disease was accepted when one of the following criteria was present: (1) An unquestionable history of angina of effort with or without the cardiographic pattern of ischemia either at rest or provoked by a test exercise. (2) Cardiographic evidence of myocardial infarction. Most patients in whom this was present gave a history of prolonged chest pain and also had the associated phenomena characteristic of cardiac infarction. That infarction was usually of at least moderate severity was indicated by the fact that more than 90 per cent of the cardiograms that showed cardiac infarction had pathologic Q waves. In the absence of other possible causes, heart block was considered to be due to coronary artery disease. (3) The finding of a myocardial infarction at necropsy.

Results

A cause of heart failure in addition to hypertension was found in all but 12 (2.6 per cent) of the 445 patients with high blood pressure.

The diseases that precipitated heart failure were considered under two main groups of causes, renal and nonrenal. Included in the group of renal causes (104 cases) were patients with evidence of renal disease alone or in combination with cardiac lesions and also patients with malignant hypertension since this condition is associated with renal vascular damage. The remainder of the patients with a known cause of heart failure formed the group of nonrenal causes (329 cases) (Table I).

In those instances in which several conditions were associated, the one most likely to place an added strain upon the heart was accepted as the factor initiating cardiac failure. Many of these associated

conditions, however excluded as immediate causes of failure, could have contributed to its development. Thus, obesity occurred in 70 patients (16 per cent) 27 patients (6.1 per cent) had diabetes mild anemia was present in 14 (3 1 per cent) thyrotoxicosis in 9 (2 per cent) myxedema in 6, prostatic obstruction in 6 acromegaly in 2 Paget s disease in 2 and cholecystitis in 2 and in 1 case each there was Buerger s disease, transverse myelitis gout scleroderma, and pemphigus (treated with steroid therapy)

Previous hypotensive therapy in 161 patients did not significantly influence the relative frequency of the causes of failure or the prognosis when compared with patients who had not received this treatment.

Renal causes

Patients in this category had primary kidney disease (e.g chronic nephritis, pyelonephritis, renal calculus, and hydronephrosis) or malignant hypertension The subgroupings were as follows

A Isolated renal disease Isolated renal disease was present in 30 patients 40 per cent of whom died at an average age of 51.2 years their total average age was 54.1 years.

B Renal lesions combined with either ischemic heart disease (30 cases) or valvular lesions (6 cases) Each of the 24 men had evidence of cardiac ischemia of the 12 women 6 had associated ischemia and 6 had valvular complications. Their total average age was 60.6 years 41 7 per cent died at an average age of 61 years.

C Malignant hypertension There were 38 patients with malignant hypertension This diagnosis was made when hypertension and albuminuria were associated with papilledema. Of the 22 men 5 had angina pectoris and cardiographic evidence of infarction in 2 myocardial farction was confirmed at necropsy Three women had angina and evidence of cardiac n farction. Their total average age was 48 8 years 44.7 per cent of them d ed at an average age of 50 7 years.

Nonrenal causes

A Cardiac ischemia. Ischemic heart disease occurred n half the patients in this series and was by far the most common immediate cause of heart failure (Table I) It probably contributed to the development of failure in a still larger proportion of patients since evidence of coronary artery disease in minor degree, was present in a number included in other groups (*vide infra*) When all such patients were included there was a 64 per cent incidence of cardiac ischemia 72 per cent of men (average age 61 years) and 61 5 per cent of women (average age 63 4 years) had either angina pectoris or a myocardial infarction

Cardiac ischemia occurred in 210 (68 per cent) of the 309 patients with diastolic pressures below 130 mm. Hg and in 78 (63 per cent) of the 124 patients with pressures above that level

Acute left ventricular failure was as common as congestive failure more often a combination of both was present.

Predominant cardiac ischemia as a cause of heart failure was associated with a mortality rate of 19 8 per cent The average age at death was 65.8 years, whereas the age of the survivors averaged 61 years.

B Valvular lesions The aortic valve, with regurgitation predominating was most frequently in ol ed in men, two thirds of whom also had ischemic heart disease. Among the 23 women lesions of the mitral val e were most common, occurring in 17 patients these lesions were followed in frequency by aortic regurgitation and stenosis One third of the women had cardiac ischemia in addition.

Ages averaged 65 years for men and 56 years for women the presence of associated ischemia gave an average age of 66 years and merely reflected the higher incidence of coronary disease among the men Without associated ischemia the average age was 55.8 years.

Auricular fibrillation was present in 52 per cent of the patients with valvular lesions, against an incidence of 21 per cent in those without valvular damage

C Respiratory infections. Bronchopneumonia or bronchitis alone was a precipitating cause of heart failure in 6.1 per cent of the hypertensive patients in this series their average age was 66 years (men 59 years, women 72 years) In the majority of these patients the acute infection was

Table II. Mortality in relation to age in hypertensive patients with heart failure

Cause	Age group (yr.)			
	<50	51-60	61-70	71>
Renal				
Number of patients	36	42	19	7
Died	16	15	10	3
Mortality	44.4	35.7	52.6%	42.9%
Nonrenal				
Number of patients	46	101	136	46
Died	6	16	24	24
Mortality	13	15.8	17.6	52.2%
All known cause				
Number of patients	82	143	155	53
Died	22	31	34	27
Mortality	26.8	21	21.9	51%

superimposed upon chronic bronchitis and emphysema. A further 51 had chronic bronchitis and emphysema but in these it was not considered to be the major cause of heart failure.

Bronchopneumonia occurred in 30 patients after the development of heart failure and in 16 of these it was the cause of death.

Although a higher incidence of right ventricular failure might be expected in the presence of chronic bronchitis and emphysema, no such bias was found. The frequency of right and of left ventricular failure was the same for those with as for those without chronic pulmonary disease.

D. Miscellaneous lesions. Diseases that precipitated heart failure in this subgroup comprised thyrotoxicosis (12 cases), anemia (7), paroxysmal tachycardia (4), paroxysmal auricular fibrillation (4), and myxedema (4). Although pulmonary embolus occurred after hospitalization of the patient and caused aggravation or recurrence of heart failure that resulted in death in 9 instances, it did not occur in any patient as an initial cause of heart failure. No significant conclusions were drawn from this subgroup of patients.

Of the 12 patients in whom no cause other than hypertension was found to account for heart failure, one, a 43-year-old woman, had a suspected but unproved renal lesion. The remainder of the patients (average age 59 years) had large hearts. In respect of age they corresponded with the nonrenal group. All 12 patients had diastolic pressures between 90 and 130 mm. Hg. None had received previous hypotensive therapy.

Cause of death. A combination of several factors contributed to the outcome in the majority of those who died. As the primary cause of death, myocardial infarction occurred in 40 patients; 30 others, all of whom had either a pre-existing renal lesion or malignant hypertension, died in uremia; respiratory infection caused death in 16, persistent heart failure in 10, pulmonary embolus in 9, and cerebral hemorrhage in 7, and in the other 2 death was due to mesenteric embolus and carcinoma of the stomach, respectively.

Prognosis

Heart failure developed at a slightly earlier average age in men (58.8 years) than in women (61.1 years). The mortality in men (27.4 per cent) was higher than in women (24.4 per cent), and the men died at an earlier age (59 years) than the women (64 years). For all patients, heart failure occurred at the age of 60 years, and 25.6 per cent died at an average age of 61 years.

Mortality was unaffected by the presence of auricular fibrillation, the size of the heart, or the type of heart failure that occurred; the proportion of patients dying

with acute left ventricular failure was similar to the number dying with congestive heart failure or a combination of both

Age exerted some influence upon the mortality rate but was far less important than the presence of a renal lesion The height of the blood pressure also appeared to exert some influence on the outcome.

A The presence of a renal lesion A renal cause of heart failure carried a mortality rate of 42 per cent the average age at death was 53 2 years. In contrast death occurred at an average age of 66.4 years in only 24 per cent of the patients with a nonrenal cause of heart failure (Table I)

B Age After the age of 70 the proportion of deaths rose considerably as patients reached their allotted span Below this age the combined mortality rate was highest in the youngest group of patients (Table II) and this rate was as high in the sixth as in the seventh decade. This discrepancy was explained by the large proportion of patients with a renal lesion (associated with a high mortality in the younger age groups) Below the age of 50 44 4 per cent of the 36 patients in the renal group died whereas the nonrenal group of 46 patients had a corresponding mortality of 13 per cent (Table II)

Among the nonrenal group of patients the mortality rate showed a slight but progressive increase with advancing years until the eighth decade when it increased threefold. Advancing age did not affect the outcome in the renal group 75 per cent of whom were less than 60 years of age.

C Level of blood pressure In order to assess the effect of the blood pressure upon the mortality the percentage of deaths was calculated below and above an arbitrary diastolic pressure level of 130 mm. Hg

For all patients with a known cause of heart failure the mortality rate was higher in the diastolic range above 130 mm Hg (Table III) Further analysis revealed that this pressure range contained a relatively larger proportion of patients with renal disease than did the pressure range below 130. Although comprising only 23 per cent of the whole series, the renal group contributed as many as 61 of the 124 patients with diastolic pressures above 130 but only 43 of the 309 patients with pressures below this level

The adverse effect of high blood pressure upon mortality was more conspicuous in women 21 9 per cent with diastolic pressures below 130 mm Hg died compared

Table III *Mortality in relation to height of blood pressure in hypertensive patients with heart failure*

Cause of heart failure	Level of diastolic blood pressure (mm.Hg)					
	Men		Women		Total	
	90-129	130	90-129	130	90-129	130
Renal						
Number of patient	24	37	19	24	43	61
Died	13	13	7	11	20	24
Mortality	34 2%	35 1%	36 8	45 8%	46 5%	39 3%
Nonrenal						
Number of patients	139	40	127	23	264	63
Died	30	10	25	5	55	15
Mortality	21 6%	25%	19 7%	21 7%	20 7%	23 8%
All known causes						
Number of patient	163	77	146	47	309	124
Died	43	23	32	16	75	39
Mortality	26 4%	29 9%	21 9%	34%	24 3%	31 5%

with 34 per cent of those with pressures above that level. In men the corresponding rates were 26 4 and 29 9 per cent Again this apparent sex difference could be explained by the relatively larger proportion of patients with renal lesions among the women who died in the higher pressure range as compared with men (Table III) Furthermore the mortality in women with renal disease and diastolic pressures above 130 was greater than that for corresponding men.

It seemed possible that the increased mortality for patients in the renal group might be accounted for by the relatively larger proportion with very high blood pressures in this group as compared with the nonrenal group This, however was not the explanation since death occurred in 46 5 per cent of patients in the renal group with diastolic pressures below 130 as compared with 39 3 per cent with pressures above 130 Indeed when renal and nonrenal groups were considered separately the height of the blood pressure did not influence the death rate in either group (Table III)

Discussion

As an isolated burden high blood pressure was an infrequent cause of heart failure in this series. Additional myocardial injury was required to initiate failure

In half the patients this additional stress was provided by cardiac ischemia, and in a further 14 per cent ischemia probably contributed to the development of failure. This is in keeping with numerous published reports in regard to the frequent association of high blood pressure with coronary arterial disease Thus, antecedent hypertension has been reported in 64 per cent of patients with coronary disease similar estimates include 58 per cent 57 per cent 54 per cent, and 41 per cent[11] —and it has been reported that hypertension precedes coronary occlusion in 27 75 per cent of cases as compared with a hypertension incidence rate of 2 11 per cent of the general population [12] At necropsy severe coronary atheroma has been found in 85 per cent of the patients with essential hypertension and heart failure but only 10 per cent of those without cardiac failure had similar coronary disease.[13]

A renal element was responsible for heart failure in 104 patients (23 per cent) in this series. The mechanism by which kidney disease induces failure is not known The height of the blood pressure might have contributed to failure in these cases since renal disease was associated with high levels of pressure 58 6 per cent had diastolic pressures above 130 as compared with 23 7 per cent of the patients in the nonrenal group This explanation could not account however for failure that occurred in the 41 7 per cent of the renal group with diastolic pressures below 130 Previous reports [14-6] have found no correlation between the grade of hypertension and the presence or severity of heart failure among patients with *acute* renal disease and similar findings have been recorded among patients with essential hypertension.[7] It has been suggested that edema of the myocardium might weaken ventricular contraction[17] Alteration of the electrolyte concentrations in the body's fluid compartments, secondary to renal disease, could explain the deficiency of myocardial contraction

The most conspicuous finding among patients with renal disease was their high mortality A renal cause of failure reduced the average age at death by 13 years and almost doubled the mortality rate in comparison with patients in the nonrenal group This high mortality was due to uremia which occurred in 27 of the 44 patients in the renal group The insidious development or aggravation of uremia was not only favored by the presence of cardiac failure but in some cases was unavoidably encouraged by the treatment which included fluid restriction

Advancing age was associated with a slight increase in mortality in the nonrenal group of patients the rate of increase however was not significant and in any event was no more than that expected for the general population of corresponding age. The adverse effects of age were greatly outweighed by the renal factor

A probable but not significant increase in mortality was found with increasing blood pressure when all patients were considered and also among the women This finding agrees with previous reports[18] in one of which[1] the height of the blood

...sure was considered foremost among ... factors affecting the prognosis in hy... tension It was possible however to ...ount for the worsening prognosis with ... of pressure by the distribution of pa...nts with renal lesions in these groups. ...rthermore the height of the blood pres...re did not affect the mortality in patients ...th renal disease in the nonrenal group ...e proportion of deaths did not rise sig...ficantly with increase in blood pressure ...able III)

The increased risk of death among those ...tients with very high blood pressure in ...is series was attributed, not to the height ... the blood pressure per se, but to the ...existence of a renal lesion The apparent ...mportance of high blood pressure was due ...o the common association between a very ...igh arterial pressure and renal disease

The recorded mortality rates for heart ...ailure as a cause of death in patients with ...igh blood pressure have averaged 48 per ...ent (1928—44 per cent 1932—50 per ...ent[8] 1935—55 per cent[3] 1941—43 per ...ent[4]) with no significant improvement ...between 1928 and 1941 This mortality rate parallels the mortality among those with renal disease in the present series whereas the 24 per cent mortality among the nonrenal group of patients with heart failure represents a considerable improvement. This reduced mortality rate could not be attributed to hypotensive therapy More likely was improvement due to measures taken to reduce the additional burdens on the myocardium e.g early and adequate treatment of myocardial infarction and respiratory infection such conditions being more amenable to treatment than renal failure which claimed such a large proportion of the patients in the renal group.

It is perhaps significant that hypotensive agents had not been administered to those in whom no precipitating cause of failure was discovered In these patients, inability of the coronary arterial flow to keep pace with the work demands of a hypertrophied myocardium probably accounted for the onset of failure It is possible that heart failure would have been avoided had they received hypotensive therapy That simple overstrain must be a major influence has been demonstrated by the virtual disappearance of hypertensive heart failure as a cause of death when ganglion blocking agents are effectively used.[20,21]

Summary

In a series of 445 patients with high blood pressure and heart failure a cause of failure in addition to hypertension was found in all but 12.

Ischemic heart disease precipitated heart failure in half the patients and probably contributed to the development of failure in an additional 14 per cent.

Other important causes of heart failure were valvular heart disease, renal disease alone or combined with cardiac lesions, malignant hypertension and respiratory infections. The other less frequent causes of heart failure were combined to form a miscellaneous group

The presence of a renal lesion as compared with no renal damage almost doubled the mortality rate and reduced by 13 years the average age at death. Patients with renal disease had the highest blood pressures. The worsening prognosis of patients with hypertension and heart failure with increasing levels of blood pressure was shown to be due to the presence of a renal lesion rather than to the height of the blood pressure per se.

I wish to thank the physicians of Charing Cross Hospital for allowing me access to their case notes. I particular I am indebted to Dr P.B.S. Fowler for permission to study patients in the Hypertension Clinic, and t Dr K. Shirley Smith for advice and criticism.

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Appraisal and reappraisal of cardiac therapy

Clinical evaluation of alpha methyl-dopa

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In 1960 alpha methyl-dopa (alpha 3 4-dihydroxy L phenylalanine) a syn thetic compound related to the catechola mines, was introduced as an antihyper tensive drug Experimental evidence i di cates that it inhibits decarboxylation of dihydroxyphenylalanine (dopa) to dihy droxyphenylethylamine (dopamine) there-by interfering with the in vivo production of norepinephrine and epinephrine, but this is probably not the mechanism by which blood pressure is reduced It is also con sidered to be an inhib tor of the decar boxylation of 5 hydroxytryptophan the precursor of serotonin (5-hydroxytrypta mine)

In the laboratory animal in which its pharmacologic effect is primarily on the blood pressure the drug is found to have low toxicity In the therapeutic range transient sedation is observed The dis-tribution of the drug in the body appears to be widespread with a high concentra tion found in the kidneys. No alteration in renal function occurs and the drug is excreted by glomerular filtration. Because of its excret on in the urine in large part unchanged it interferes with the measure ment of urinary catecholamines. The urine on standing develops a dark color which is due to the oxidation of alpha methyl dopa similar to homogent sic acid or melan n precursors.

Other than on blood pressure this agent has no apparent autonomic act on thus differing from ganglionic postganglionic and peripheral blocking drugs.

Clinical data on the effectiveness of alpha methyl-dopa as an antihypertensive agent have been reported by investigators in many countries. The great interest shown in this compound is manifested by the fact that at the recent World Congress of Cardiology held in Mexico City in October 1962 there were eleven papers relating to this drug Unfortunately the drug has not been carefully studied in comparison with other antihypertensive agents, so that its proper place in therapy has yet to be determined. In general it would appear that a satisfactory lowering of blood pressure can be obtained in pa tients with mild or moderately advanced hypertension The blood pressure is reduced both when the patient is supine and when he is standing However in severely hyper tensive patients, particularly those with malignant hypertension guanethidine or one of the other powerful blocking agents may be required. Also it has been noted that the combination with one of the thiazide drugs is desirable, not only to enhance the antihypertensive effect but also to counteract the retention of sodium with increased plasma volume which is noted qu te often when alpha methyl-dopa is given alone for long periods.

Enthusiasm for alpha methyl-dopa as an antihypertensive agent varies widely some observers claim almost 100 per cent ef fectiveness, whereas others cla m only 40 per cent. The choice of patients obviously

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influences the results. In general the results appear to be better in the mild cases, although some excellent results have been reported in the severe or malignant forms of hypertension

Hemodynamic studies in man show a decrease in cardiac output but no decrease in renal blood flow There is a slight decrease in peripheral resistance

The dosage used ranges from 0.5 to 4 0 Gm per day However it is generally conceded that there is no increased therapeutic effect on exceeding 2 0 Gm per day The usual dose is 250 mg four times a day—a total of 1 0 Gm per day The hypotensive effect appears promptly and when the drug is withdrawn the return of hypertension appears with equal promptness (within 24 hours) even though the drug has been given daily for many months. Although some instances of drug tolerance have been reported tolerance in general is not observed even after several months of use

The major side effect is drowsiness, which appears quite early in the treatment and occurs in about 50 per cent of the cases. A reduction in the dose will decrease this side effect. Other side effects which have been noted are dryness of the mouth nasal stuffiness, nausea, diarrhea impotence headache weakness, and mental depression These are all minor however and a reduction in dose usually decreases or eliminates them One case of thrombocytopenia has been reported and there are also reports of occasional skin rash With these complications, of course the drug must be discontinued Acute hepatotoxicity of the type seen with chlorpromazine has been noted. Fortunately in the instances known to us withdrawal of the drug has resulted in complete disappearance of evidence of liver toxicity In rare instances, ochronosis may develop on prolonged therapy The retention of fluid which is due to expanded plasma volume and the retention of sodium can be easily counteracted by the use of small doses of one of the thiazides.

Although it is too early as yet to determine the exact role of alpha methyl dopa in the treatment of hypertension there is enough evidence to indicate that this drug will be a desirable adjunct to antihypertensive therapy particularly in combination with other agents

Generic and trade names of drugs: alpha methyl-dopa—Aldomet; guanethidine—Ismelin.

Annotations

The fatal illness of Napoleon the Great

The political atmosphere For the understanding of the reasons which have obscured the real nature of Napoleon fatal illness t St Helena and of the adoption of the extremely doubtful iew that Napoleon suffered nd died of cancer the political tmosphere encompassing Napoleon exile and life at St. Helena has to be considered.

England was governed by the Tory government of Lord Liverpool who exiled N poleon to the tropical and insal brious island of St. Helena, after removing the Governor of the island, General Wilks, who was considered to be amenable to the influence of N poleon, and ppointing as his suc cessor Sir Hudson Lowe, of whom even defender of Lord Liverpool government, Rosebery tells "The erdict of History is niformly unf ourable.

Hudson Low subjected his august prisoner (whom he persisted in calling General Bonaparte forbidding everyone to designate him as Emperor Napoleon) to many cruelties and humiliations and showed a complete indifference to the health and hygienic conditions of the Emperor This caused general popular outcry in England and on the Continent, and it was in the terest of Lord Liverpool" government to allay this opposition by hiding the real nature of the illness of Napoleon hich from the beginning showed the features of tropical disease The first physicia ho ttended the Emperor the naval surgeon, Barry O'Meara dared to make the diagnosis of tropical hepatitis and to point out the deleterious influence of the climate of St. Helena. H as arrested, court-martialed, sent back to England and struck off the Na y List His successor Dr Stokoe also na al surgeon had the cou age to make the same diagnosis and was also court-martialed nd dismissed from the N vy. The third physician, Dr Antommarchi, sent by the family of Napoleon greed with his predecessors but could not be dismissed by Hudson Lowe. Only the fourth, Dr Arnott military surgeon sent on the demand of A tommarchi to onfirm his opinion about the dangerous condition of the Emperor made the diagnosis of simple hypochondria — eighteen day before Napoleon breathed his last

Even the postmortem was somewhat bungled officially to show that Napoleon did not suffer from tropical disease The official report signed by four naval nd military surgeons tells of exten si cancer of the stomach all other organs, par ticularly the l er being intact The most distinguished of these four representatives of Hudson Lowe, Dr Thomas Shortt, protested, nd in a separate report indicated that the liver was enlarged, but he was ordered to suppress these words. H kept a copy of his original report and wrote in the margin of the obliterated sentence "These words were deleted, by order of Sir Hudson Lowe.

These were the methods through which Hudson Low endeavored to hide the true nature of the illness of Napoleon, an illness which lasted, w th intermittences, fi years. Unfortunately this partisanship has been reflected in some historians ho have ttempted, without shred of evidence, to blacken the reputation of the physicians ho maintained the diagnosis of tropical disease and to cast doubt on the eracity of their writings, as ell as on the faithful and detailed diaries and writings of the French ttendants of Napoleon. For this reason this problem has to be rein estigated, the more so that very recently evidence from two important witnesses, General Bertrand and General Gourgaud, has been published.

The physicians of N poleon. Barry O'Meara, a na al surgeon medical graduate of Trinity College, D blin was the first physician attached to Napoleon and ttended him from his arrival in St. Helena until 1819 hen, as he reported that Napoleon suffered from tropical hepatitis and that the climate of St. Helena was aggravating his condition—an opinion that did not suit the interests of Hudson Lowe—he as arrested, court-martialed, sent back to England and struck off the Navy List. He was deeply attached to Napoleon and appears a good physician and courageous man. Naturally the official historians have ttempted without a shred of evidence, to blacken his reputation.

Dr John Stokoe surgeon t "The Conqueror stationed t St. Helena succeeded him. After the departure of O'Meara in July 1818, Napoleon, although ill, refused t see the doctors appointed by Hudson Low considering them as spies politically and medically incompetent. However on Jan 18, 1819 on account of serious attack, Dr Stokoe, who is described as clever doctor and honest man was received. He attended Napoleon only few da s, because as he drew up report agreeing ith the diagnosis of tropical hepatitis he was immediately as stated above, arrested court-martialed, sent back to England and dismissed from the N vy

Dr Francesco Antommarchi was the third physician ho ttended Napoleon f om September 1819 up to his death. After the departure of Stokoe Napoleon asked his family to send him trusted

medical attendant, sending them at the same time a report about his illness, and, after careful search, Antommarchi was chosen and Lord Liverpool's Government allowed him, with some reluctance, to go to St. Helena to attend the Emperor. He was an outstanding physician, a graduate of the great University of Pisa, appointed by Pietro Mascagni, one of the greater leaders in anatomy and pathology in those days, as his assistant and later as prosector in Florence. Before going to England, Antommarchi was examined by the professors of the Faculty of Medicine of Rome, with whom the illness of Napoleon was discussed. His observations of the symptoms of Napoleon's illness point out a skilled clinician, and his report of the autopsy—the only reliable and detailed report, according to Arthur Keith and Arnold Chaplin—shows a remarkable descriptive power, a knowledge of pathology great for his times, and scientific sincerity. Before all these facts, the accusations of certain historians—including Lord Rosebery—appear a figment of imagination. Antommarchi agreed with his predecessors as to the diagnosis of Napoleon's illness but of course Hudson Lowe could not remove him.

The fourth physician connected with Napoleon was Dr. Archibald Arnott, a military surgeon who attended Napoleon together with Antommarchi from April 1, 1821, up to the date of the death of the Emperor. In fact, since Antommarchi considered that Napoleon was suffering from a fatal disease, whereas Hudson Lowe maintained that he was simply malingering, he asked for a governmental doctor to visit him. Arnott was sent and *after examination of the patient told on April 17* Sir Thomas Reade, the head of the forces in St. Helena, that the disease was "Hypochondriasis" and that "if a 74-gun frigate appeared at bay to set him at liberty, Napoleon would be up and on his legs directly."* Eighteen days after, Napoleon breathed his last.

Clinical history. The clinical history of Napoleon's fatal illness gives us the key to diagnosis. It can be reconstructed thanks to the writings and diaries of Napoleon's physicians, particularly those of O'Meara and of Antommarchi (these last showing a talent for clinical observations) and also of his French entourage: General Bertrand, General Gourgaud, Count Las Cases, Count Montholon, and of the faithful valet Marchand. The exactity of these reports has been denied by certain authors but, as practically all of them agree—except on certain minor details, particularly dates—this argument cannot be accepted. It is of course difficult to wade through the maze of all these writings, but I have been greatly helped by the recent publication of Dr. Forshufvud, who has given us the *most conscientious and detailed description of* Napoleon's illness, whose views on arsenical poisoning are, in my opinion, somewhat speculative because it is difficult to accept such a prolonged (six years) poisoning of the Emperor, surrounded by faithful attendants and taking his meals with them. The clinical history, notwithstanding the efforts of Dr. Forshufvud, do not confirm arsenical poisoning, and as for the *findings of large quantities of arsenic* in the alleged hair of Napoleon, how many errors have been committed in forensic medicine with such determinations!

Napoleon was practically always in perfect health and endowed with a great physical resistance. He was in perfect health during his long journey from France to St. Helena. However, a little more than one month after his arrival in that island his long-drawn illness began. This illness was characterized at first by intermittent attacks separated by intervals of good health, the attacks becoming progressively more severe and the intervals of good health shorter. About July, 1820, the intervals of health were usually incomplete and the disease was assuming a more or less permanent form.

The symptoms noted during the attacks were general fatigue and particularly weakness in the legs, shivering and fever, intense headache, sleepiness or insomnia, yellowness of skin and eyes, pain often unbearable in the hepatic region and twinges on the right shoulder, dry cough, nausea, enlargement of the liver, constipation followed by diarrhea. Only in the last days—after the administration of antimony—did gastric symptoms of vomiting and, once or twice, hematemesis occur. These symptoms pointed, in those days, to what was called "tropical hepatitis," and the modern clinician will recognize amebiasis, in its frequent constitutional and hepatic form, such as I have often observed in the Near East. A special feature is that such patients do not lose weight, and it should be remembered that Napoleon—as remarked even in the *Hudson Lowe* postmortem report—maintained his corpulence until near the end. (This is certainly not a feature of an extensive cancer of the stomach.) On reading the reports, one is struck by the tremendous courage and vitality with which Napoleon was fighting his five-year illness. For the sake of clearness, this illness will be described chronologically.

1815. The first manifestations of illness occur on November 25, when Bertrand and Gourgaud note that the Emperor is very ill. On December 28, another bout of illness, and Las Cases notes that the health of the Emperor deteriorates. No medical details are given.

1816. This year Napoleon's disease is well manifested. Severe attacks occur in May, July, August, September, October, and December. These attacks last about one week or more and are separated by periods of good health. They are characterized by general fatigue and weakness, particularly in the legs, headache, fever, photophobia, pain in the right hypochondrium, yellow appearance (Bertrand), colic (O'Meara), dysentery (Marchand). O'Meara *thinks of hepatitis*. There are also troubles with the teeth. Napoleon feels that he is suffering from a tropical disease and tells O'Meara: "The slow torture, the killing in detail, is much less humane than if they ordered me to be shot at once."

1817. These intermittent attacks continue and appear more severe. On January 26, Napoleon leaves the house for the first time in two months. *Attacks are noted in March (with diarrhea, according to O'Meara),* in May, in September. Symptoms are similar to those of 1816, except that the pa

*Lowe Papers. Vol. 20, p. 137

in th hepatic region more hara teristic (O'Meara) and on October 3 O'Meara finds the liver definitely swollen. Constipation nausea and great depression are noted.

1818 The illness continues with ups and downs but there is ot m ch information for this year In July O'Meara draw p a report on the condition of the Emperor indicating that he is suffering from tropical hepatitis and giving as his opinion that the limate of St. Helena is deleterious for him. Following this report, he is arrested by Hudson Lowe court-martialed, sent back to England on July 25 and dismissed from the Navy Thus, in this critical phase of his illness Napoleon is deprived of his trusted physician. Attacks are noted in October and December—same symptoms head aches often unbearable, palpitations, sensations of fever stomach ache and nausea, diarrhea (' Oc tober according to Bertrand), swelling and pain in the hepatic region are reported. On the hole, however in "The end of the ear the condition seemed improved.

1819 In the night of January 16-17 severe ttack, giddiness, fainting fever pains in the hepatic region and sharp twinges in the right shoulder Dr Stokoe is sent to him, notes these symptoms and notes particularly the intense pain provoked by a slight pressure on the hepatic region. H draw up bulletin, indicating hepatitis as his diagnosis and giving also as his opinion that the climate of St. Helena is dangerous for the ugust patient. After this report, Hudson Lowe forbids Dr Stokoe to set Napoleon again, court-martials him, and sends him back to England. Although S okoe had only few months before retiring on full pension he was dismissed from the Na y immediately thus with half pension. In the height of severe ttack of illness Napoleon is deprived of medical ttention. At all events, the ttack terminates and is followed by period of recovery til August hen another severe attack occurs. Napoleon asks for Stokoe, who has not yet left the island Hudson Lowe, however refuses this demand

Dr Antommarchi—sent by the family of Napoleon—arrives in September H notes (in his diary for September 23) hardness of hearing face ashy pale, conjunctiva reddish-brow mixed w th yellow corpulent body coated tongue. Pulse 60 regular Part of left lobe of the li er touching on epigastric region hardened and extremely painful on palpitation. Bouts of nausea and omiting Abundant sweats weakness of legs. On October 15 pain in the liver worse than ever

1820 The first months are good, but on July 19 beginning of severe ttack which lasts about ten days and is characterized part from the general symptoms, by pain in the liver particularly acute spreading to the right shoulder

On September 18, another severe ttack, which marks the beginning of an aggra ation of the condition same symptoms w th perhaps more distinct yellowness of the skin and epigastric pain. Some relief but another attack from the October 10 to 18 and from October 25 t November 5 N great relief between the ttacks. Some general and abdominal symptoms. Constipation, followed by diarrhea.

1821 The illness has assumed a more permanent form. Napoleon does not lea his room. In January colic followed by diarrhea. On February 6, ttack with omiting sensation of burning in the intestines pain under the left nipple, thirst. On March 1 severe ttack with fever chill, pain in the hepatic region. Without the knowledge of N poleon antimony (¼ grain) is administered in lemonade and is followed three quarters of an hour after by iolent omiting of glairous matter and rolling bout the floor contorted with agony Gastric ymptoms occur more intense. On the demand of Antommarchi, who considers N poleon condition fatal, governmental doctor Arnott, is sent on April 2. H diagnoses hypochondria and probably gastritis. On April 3 omiting of black matter The temperature of the gust patient is taken and found to be 35°C. (95°F). On April 20 Napoleon feels better H gets up alks sits for dining, eats meat and, on the whole more than for long time, and keeps his food. H tells the doctors that he feels stronger but on April 25 in the night iolent burst of omiting hematemesis, melena. This omiting continues the next days, and Antommarchi writes "he is in the last stages of prostration. N poleon tells Montholon Pity me I m done for He is racked with fever On M 1 Montholon tells that Napoleon dictates for tw hour and then asks for the Abbé Vignali and receives the last sacrament. Later in the day however some delirium. Hiccups occur On May 4 Arnot dministers against the advice of Antommarchi, but with the support of tw naval surgeons sent by Hudson Low ten grains of camomel (the maximum in our Pharmacopoeia is 3 grains). Prostration follows con ulsive movement, agony rattle On May 5 t h and three quarters the great Emperor breathes his last.

The Postmortem The autopsy of Napoleon took place bout twenty-four hours after his death nder difficult physical conditions and under conditions of mental tension. It was done in the so-called drawing-room of Longwood, room 15 feet by 18 feet, green painted and dimly lighted by only tw indow on one side only None of the h giene conditions necessary existed The body was rapidly decomposing in that hot climate the heat was tifling nd there was not sufficient quantity of water

Apart from Dr Antommarchi, the onl pathologist present, who performed the topsy there ere present among the courtiers of N poleon, General Bertrand, Montholon the ttendants Marchand Saint Denis, Pierron the Abbé Vignali, and as representati es of Sir Hudson Low (ho had excused himself) Lt. Col. Sir Thomas Reade Major Harrison Captai Crokat, five naval or military surgeons, Shortt Arnott, Mit hell, Burton and Livingstone and two assistant surgeons R t ledge nd Henry A rather large crowd of t least seventeen shut into small room. There as a dramatic tension between the French and the British group. The French expected to find evidence of tropical disease to accuse the uthorities for the treatment of the Emperor and the British wa ted t ll costs, to old y such finding

The topsy la ted from 2 to 3 45 P.M. The heart

and stomach were removed and placed in a special *receptacle but this was replaced in the coffin al*though Antommarchi begged to have the stomach. At the end of the autopsy the body was sewn up by Antommarchi and Sir Thomas Reade representative of the Governor ordered Dr. Rutledge *and Dr. Arnott to guard the body carefully not to* lose sight of it at any moment, and to pay particular attention against anyone opening it again and removing any of the viscera.

It is on the results of the postmortem that violent discussions have taken place. One should remember however that whereas in our days pathology with the advanced knowledge of the macroscopic aspects of lesions and principally with the microscopic examination gives the key to diagnosis, this was not the case in 1820 because the microscope was not applied and the macroscopic aspect of lesions was not well known, morbid anatomy being in its beginning. This explains the hesitations and contradictions of Antommarchi who, being the only pathologist of the group was conscious of the imperfections of the new science. With these reservations the three reports of the autopsy can be considered.

The official report need not detain us. As Keith writes, "Every medical man knows that the official report cannot be true." It was signed by the four military and naval surgeons who undoubtedly did not possess any knowledge of pathology and were under the orders of Hudson Lowe. Even among these four the most competent Dr. Shortt disagreed, *but had to obey orders. In fact*, this short report reads like a military order and describes the whole stomach invaded by cancer all other organs being healthy!!

The report of the young assistant surgeon Henry can also be set aside. It was written from notes more than two years after the death of Napoleon and addressed to Hudson Lowe to help him defend *himself* against the attacks to which he was subjected after his return from St. Helena. Written in a flourishing and somewhat juvenile style, it gives strong evidence of partisanship. Henry describes in this sense a "Mass ( ) of cancerous ulceration" and adds something that is a real gem. He describes the body of Napoleon as "Slender and effeminate" and writes that penis and testicles were very small and "the whole genital system seemed to exhibit the absence of sexual desire which has been stated to have characterised the deceased." Napoleon chaste! What a distortion of history. And can we visualize the young naval surgeon in the middle of that dramatic tension *measuring the penis and testicles of Napoleon!* What a vivid imagination. The report of Antommarchi is, in the words of Arthur Keith and Arnold Chaplin, "the most complete and reliable document." It is written in a real scientific spirit and describes accurately what was seen without any flights of imagination or bias even regarding his own ideas of Napoleon's *illness*. It can be considered as a model of autopsy report for those days. Antommarchi notes effusion of liquid in both pleurae. He describes the enlargement of the liver and adds with sincerity that "the tissue of the liver which was reddy brown in colour did not, however present any other notable altera-tion in structure." (Of course, alteration of liver *tissue indicating hepatitis cannot be detected* macroscopically.) He notes the small spots and patches on the peritoneal surface of the digestive canal (intestine). He describes the gastric lesion in detail: a cancerous ulcer which had its centre *at the superior part along the small curve of the* stomach communicating with the liver. Having knew the state of the science of morbid anatomy in those days, one can only admire the precision and the power of observation shown in this report. Antommarchi expressed later doubts about the cancerous lesion but these were the doubts justified in a scientist who realizes that macroscopic examination in days in which even the macroscopic features of a cancerous lesion were not well known, did not allow a definite opinion principally when the clinical history was against the diagnosis of cancer. In fact, he had asked to preserve *the stomach for more precise examination* but this was refused.

The specimen in the museum of the Royal College of Surgeons. Until the bombing and fire of the Royal College of Surgeons in 1941 fragments of small *intestine considered as originating from Napoleon's* autopsy were preserved. These specimens were given by Antommarchi to O'Meara and by O'Meara to Sir Astley Cooper. On the death of Sir Astley Cooper they passed with the rest of the great Astley Cooper collection to the Royal College of Surgeons. In the manuscript catalogue of Astley Cooper they are listed as "Incipient Fungus of *the glands of intestine Napoleon.—Barry* O'Meara to Sir Astley Cooper."

The authenticity of these fragments has been denied by the partisans of the cancer theory because, as they were in the possession of Antommarchi, they had to be removed by him during the autopsy and this was impossible, on account of the strict supervision. Was, however the supervision so strict? Sir Arthur Keith who has made a good study of this problem considers that it could not be. Seventeen persons shut in to a relatively small room badly aerated, stifling with heat, lacking in water and other hygienic amenities, with a *corpse rapidly decomposing in this hot climate* and thus stinking, could not be always attentive. Particularly after the word "cancer" had been pronounced—an agreeable surprise to the officials—many must have wandered out to breathe some fresh air. Antommarchi, who was very skilful, and who was performing the autopsy may well have been able to subtract these small fragments which *seemed to point to a tropical disease*. It could not be very difficult. Arthur Keith writes that in the interests of science against prejudice I have known cases where great parts of the body were removed under the most strict surveillance. Furthermore, Astley Cooper was not a man to catalogue the intestinal fragments as belonging to Napoleon if he was not convinced of their origin. As the greatest surgeon in England the friend and medical adviser of Lord Liverpool he was probably the only man in England enabled to obtain first-hand informa-tion *about the illness and postmortem of Napoleon*. As a man of great judgment and sincere character he was the last person to deceive himself or wilfully

deceive others when in quest of truth. These intestinal fragments show the inflammatory patches described by Antommarchi in his autopsy report. If they did not really come from Napoleon body someone must have found similar lesions in another autopsy and passed them to Astley Cooper as originating from Napoleon. All this verges on the ridiculous but shows unfortunately the line of argument of the defenders of the cancer theory. No shred of evidence but they cannot be genuine. Barry O'Meara, Antommarchi, Lord Moynihan are liars! Astley Cooper has been led up the garden path or someone must have added the word Napoleon to the catalogue. Arthur Keith has accepted their genuineness, but as he cannot be considered as an unreliable and untrustworthy scientist, his work, his Hunterian Oration have been passed in silence. Astley Cooper considered these lesions as cancerous, but Shattock, Curator of the Museum of the Royal College of Surgeons, examined them histologically in 1909 and concluded that they were not cancerous, but simply inflamed lymphoid follicles such as occur in certain tropical diseases. Sir Arthur Keith studied also these fragments and made of that study the subject of his Hunterian Oration in 1913. His conclusions are those of Shattock, and macroscopic and microscopic figures are given abundantly in that oration. René Leriche—skilled in pathology as well as surgery—to whom they were shown by the then President of the Royal College of Surgeons Lord Moynihan has given as his opinion that they were of amebic origin.

Comment. The clinical history of recurrent attacks with the symptoms described above point out amebiasis. A textbook description such as that in Cecil and Loeb's book covers practically the whole picture. Diarrhoea is a common but by no means constant symptom. About one third of the patients do not have it, often alternating with constipation, in many cases the latter the prominent symptom ... omiting unusual, but nausea in certain cases, abdominal distress, distention, abdominal pain in the right side. Constitutional symptoms often accompany the gastrointestinal manifestations and often overshadow them. They include undue fatigue, fever (most often not high), vague somatic aching, backache and arthralgia. There may be also nervousness, irritability or dizziness, loss of weight is not characteristic ... hepatic symptoms of abscess are a frequent complication.

Amebiasis was endemic in St Helena. In Napoleon's household it was manifested in Bertrand, and the butler Cipriani probably died of it. Antommarchi, visiting the hospitals of St Helena, tells that ... (for the majority of the patients suffered from dysentery), which caused great morbidity and mortality among the forces stationed at St Helena—a fact which Hudson Lowe tried to hide from the British Government. The autopsy on account of the conditions under which it was performed and of the imperfection of pathology in those days, particularly the lack of microscopic investigation cannot give us any absolute information, but according to the only reliable report, that of Antommarchi, certain factors confirm amebiasis. Such are enlarged liver, inflammatory spots on the intestines, involvement of the pleura and possibly perforation of a left-lobe abscess in the stomach—it should be remembered that the left lobe was found hard and painful. Being sincere Antommarchi speaks of a cancerous ulcer—for what that meant in those days—but seems to hesitate and asks to keep the stomach for further examination. This is refused. The officials were only too pleased with that vague autopsy discovery which whitewashed Lord Liverpool's government. Pathology was only at its beginning; microscopic investigation which gives us the key to diagnosis was nonexistent, and the macroscopic aspect of pathologic lesions was not advanced. The term cancerous ulcer could have meant any extensive lesion of the gastric mucosa (including the usual postmortem necrosis (after 24 hours in the heat of St. Helena!) It could have meant a perforation from an abscess of the liver or a gastric ulcer (Cruveilhier described the macroscopic features of this disease only twenty years afterward) and not necessarily an ulcerated real cancer without metastases! One had to rely more on the clinical history in those days because pathology could not give a definite answer. Even in our time it is difficult to distinguish a gastric ulcer from an ulcerated cancer without microscopic examination. The inflammatory spots on the intestines which were considered to be cancerous by Astley Cooper were later proved to be noncancerous through the microscopic investigations of Shattock and of Arthur Keith.

All this points out that the representatives of Hudson Lowe, availing themselves of the presence of a gastric lesion pronounced dogmatically the word cancer and this view was defended later with passion, by violent accusations of lying and incompetence against its opponents, for political reasons. We can only share the doubts of Antommarchi. The official view of cancer goes against the clinical history and is undoubtedly not confirmed by the postmortem.

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The thermodilution method in the diagnosis of cardiac malformations and valvular disease

In recent ear the Stewart Hamilton method ha become routine proced re in the alua ion of cardiac malforma ions nd rheumatic heart disease The great number of est agen sed nd the man modification of this method indicat however ha there n ideal procedure t

When ld mployed indicator several disadv ntages of other test agent re oided Two t h milli ters of normal saline solution (temperature $-0.5°C$ t $+0.5°C$) are injected Using n NTC-resistor (negativ temperature coeffic the time-temperature curv is deter mined and recorded af er ppropriat amplifica tion. Changes in temperature of 0.01°C, result in deflec ions of abou 50 mm. The minut NTC resist ors can be easily installed in needles of gross diameter of 0.8 mm as well as in Cournand cath ters of ny given gauge

In de ecting and localizing shunt nd regurgi ta ions, one must hoose the recording si according to the particular circumstances of the case. In left-to-right shunt he cold solution is usually injected int the pulmonary artery and he NTC resistor is put close t the sit of the suspected de fect This is important since the less admixed the shunted blood is the sit of measurement the more easily are small shunt detected If mixing is complete, he time-temperature area is directly proportional to the amou t of the cold sol tion injected the temperature difference, and the shunt volume It is in ersely proportional t the squared cardiac output. The area of the time-temperature curv is, therefore, ery small when there has been much mixing This area cannot be enlarged un limitedly by increasing the sensitivi y because of hanges in temperature due t respiratory excu sions.

These changes in temperature due t respiration do not occur in the left side of the heart nor in the arterial system. In right-to-left shunt peripheral artery is chosen the point of measurement. In infants, reliable arterial puncture using large-gauge needle through which the NTC-resistor can be inserted will often pro impossible. In such cases the thermodilution method permits localiza tion of the artery w th a fine thermistor needle (diameter 0.8 mm.). It is unnecessary t ascertain t position in the lumen of the essel by measure ments of pressure or aspiration of blood.

Beyond the detection of sh nts and regurgitations it is possible t determine the cardiac output by measurement from the pulmonary artery or peripheral artery In order to determine the end-systolic volume of the right entricle, measure ments are taken from the pulmonary trunk—the indicator agent is injected int the entricle in phase with the cardiac action. The end-systolic volume of the left entricle may be determined by an analogous procedure

Critics have questioned the accuracy of quanti tativ measurements by the thermodilution method suggesting that the indicator i.e. cold may be lost to the surrounding tissues. Comparison w th meas urement by other techniques did not support these objections. Possible errors due to direct contact of the thermistor with the injection catheter can be voided by changing the site of the former

The thermodilution method is suitable for detec tion nd localization of minute shunts which cannot be elicited by gas analysis. It also permits reliable determination of m ut valvular insufficiencies. In dubious cases it is also possible to distinguish functional murmurs from accidental ones. Since there i no complete mixing the thermodilution method—like all other dilution methods—does not permit exact quantitative determination of left-to-right shunts and of regurgitations.

I comparison w th other dilution methods the thermodilution method offers the following ad vantages Initial expenditure on apparatus and operating costs are ery low compared with dilution methods employing isotopes, dyes, or hemoglobin. There are no toxic effects, no exposure to radiation, and no annoying staining Without inconvenience or danger to the patie t the injection may there fore, be repeated as often as indicated.

Because the thermistor lies in the heart or in vessel, costly constant volume pumps used for drawing samples of blood are not required. There is no loss of blood a particular advantage in infants.

Errors due to the time-lag imposed by the aspiration of samples of blood through catheter do not occur

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Interference dissociation, and semantics
A plea for rational nomenclature

The confusion which characterizes terminology in the field of trioventricular dissociation[1-4] terms from misunderstanding or misdefinition of one word—the important term interference

The word was first used in this context by Mobitz,[5,6] who coined the phrase Interferenzdissoziation to describe trioventricular dissociation caused by the discharge of an ectopic pacemaker Careful perusal of this paper lea es no doubt that Mobitz meant the term interference to refer to the effect of the discharge of the ectopic pacemaker in halting the spread of the sinoatrial impulse either by "head-on cancellation or by production of refractory state in the conducting tissues. The ord Verkettung or linkage was used to describe the occasional sinoatrial impulses conducted to the ventricles in the course of i terference-dissociation. Later common usage changed this to Ventricular capture.

Thus, two mechanisms can be defined either of hich ca produce trioventricular dissociation of arying degrees. These two mechanisms, trioventricular block and interference-dissociation, differ drastically in prognostic, diagnostic, nd therapeutic implications. The term, trioventricula dissociation therefore, becomes generic term about in the class of trial arrhythmia It is not suitable for clinical use because t is not sufficiently restrictive. Scherf[7] then either misunderstood or deliberately altered the meaning of the ord terference. He used the term to describe ventricular capture, coining the phrase dissociation with interference to fit this usage. I this same paper Scherf stated that dissociation was not produced by interference but that interference became possible because of dissociation.

*See Addendum.

When the word interference is distorted to describe ventricular capture this statement is true In the proper sense of the ord, it is not.

Tw sources of confusion are inherent in Scherf system First, the word terference is no longer used to designate the causativ mechanism of the arrhythmia t is used instead to describe an unimportant bit of byplay Whether occasional ventricular captures do or do not take place is not fact of great pragmatic significance It does not need to be indicated in the title of the arrhythmia. Second, the really significant differentiation between dissociation due to trioventricular block and that due to interference is omitted w th the generic term trioventricular dissociation pplied indiscriminately to both mechanisms

Imagine as parallel the term venereal disease being employed both as generic term nd as *the* specific term for syphilis. Imagine further the term syphilis being deprived of its present specific meaning and restricted to those cases with mucous patches This curious misuse gained moderately wide acceptance was occasionally defended with some heat if not always with logic, and has ppeared i some of the best recent texts.[8]

Appalled by the confusion in terminology some of the leading observers in the field abandoned the term interference-dissociation [9,10] and fell back on the basically undefensible use of "atrioventricular dissociation in both generic and specific sense. Confusion was further compounded when the same observers proposed the terms "incomplete and complet " trioventricular dissociation to describe interference-dissociation with nd without ventricular capture. Again relatively minor distinction is indicated in the name, hereas the really important differentiation—between trioventricu-

lar block and interference—is forgotten. What a lapse! Even more unfortunately the same set of terms is commonly applied to a very significant distinction—that between complete and incomplete atrioventricular block. The possibility of misunderstanding at a dangerous clinical level seems obvious. In the most recent edition of one of the best texts in the field, the term "complete atrioventricular-dissociation" is used to indicate *both* complete atrioventricular block and interference dissociation without ventricular capture whereas "incomplete atrioventricular-dissociation" is used for *both* partial atrioventricular block and interference dissociation with capture. Surely the resources of the language are not that easily exhausted!

Good reviews of this subject have been written in recent years delineating the two concepts of the word "interference."[4,8,9] None however seem to have caught the point in history at which the word was emasculated or to realize the significance of this semantic deviation. Schott, while describing the two applications of the term indicates a preference for Scherf's definition i.e. that in which the word refers to ventricular captures. He defends this usage on historical grounds but on precisely this point he commits a real *gaffe*. He appeals to Mobitz original work as his source. In fact, Mobitz never said anything of the sort. In any case "history" would be a poor excuse for inexact language. (Some of Schott's quotations from other sources are so handled as to verge on the disingenuous.)

Proposed classifications. Two solutions present themselves. Marriott suggests dropping the term "interference-dissociation" entirely using "atrioventricular dissociation" to designate this phenomenon specifically. Atrioventricular block of any degree is described as atrioventricular block, not dissociation and the term "ventricular capture" is used in its proper sense. Although this is reasonable, a more specific descriptive system is available which has been used for years. Miller and Sharrett employ this latter system in what this writer considers the best review of the mechanics of interference-dissociation ever written.

Several facts are considered. First, atrioventricular dissociation does actually exist as a phenomenon and is, in fact, produced chiefly by one of two mechanisms, i.e., either atrioventricular block or the discharge of an ectopic pacemaker. (For practical purposes, one may here overlook the dissociation which accompanies ventricular tachycardia, etc.) Second "interference" also exists as a well-defined electrophysical phenomenon and is actually the mechanism of dissociation in these arrhythmias (e.g., in interference dissociation.)

Finally the term "atrioventricular dissociation" has a long history of generic use to describe either of the aforementioned mechanisms.

With these considerations in mind the following system of nomenclature is proposed:

1. The term "atrioventricular dissociation" is to be discarded for purposes of clinical diagnosis and relegated to a generic sense, about in the class of "ventricular arrhythmia."

2. The term "atrioventricular block" is to be used for atrioventricular block of any degree, as in Marriott's system.

3. The term "interference-dissociation" is to be used to indicate dissociation of atrial and ventricular rhythms caused by the discharge of an ectopic pacemaker. (Since the word "interference" describes the mechanism by which the ectopic pacemaker produces the dissociation, the term seems to be appropriate.)

4. The term "ventricular capture" is to be used to describe those beats in which the impulse from the sinoatrial node reaches the ventricles, thus interrupting the discharge of the ectopic pacemaker.

5. If two ectopic pacemakers are discharging simultaneously producing an interference phenomenon, the lower of the two anatomically is to be termed the "interfering" pacemaker. (Obviously many subclassifications will be included under "interference-dissociation" such as "isorhythmic," "with or without ventricular capture," etc. These will all follow logically if the basic system is adequate.)

This system retains the useful word "interference" in its proper electrophysical sense. It does away with the vagueness which shrouds the term "atrioventricular dissociation," relegating the phrase to its proper semantic niche *as a generic term*. Finally, the cause and mechanism of the arrhythmia are indicated in the name—one of the goals of adequate medical terminology. In either system the lamentable use of the word "interference" to describe ventricular capture is discarded.

Summary and conclusions. A review of the terminology in the field of atrioventricular dissociation is presented. The various semantic aberrations which have proliferated in this regard are described and a system of terminology is presented. It is suggested that official adoption of such a system would be of considerable benefit, both at clinical and theoretical levels.

Addendum. The original text of some significant portions of Mobitz' original article is reproduced here since misunderstanding and mistranslation of this paper have been common.

"Hingegen scheint es häufiger zu sein, dass eine frequente Reizbildung im Aschoff'schen Knoten zu eigenartigen meist unvollständigen Dissoziationen zwischen Vorhof und Kammer führt." The author points out that a rapid impulse formation in the atrioventricular node is the cause of this type of dissociation between atria and ventricles. (p. 258)

"Da weder eine Störung der Leitung noch eine Herabsetzung der Reizbarkeit den hier zu schildernden Dissoziationen zugrunde liegt: ihre Entstehung und ihr Grad vielmehr durch die Art, wie Sinus-und-A-V-Rhythmus miteinander interferieren, bedingt sind, erscheint es zweckmässig sie als Interferenz-dissoziationen zu benennen." The author explains that the cause and degree of dissociation depend on the manner in which the sinus and atrioventricular rhythms interfere with each other rather than on any disturbance of conduction: hence the name "interference-dissociation" seems to be appropriate. Although the phrase "miteinander interferieren" is a little vague there is no escaping the fact that the author is talking about the *cause* of the dissociation, the interference set up by the atrioventricular nodal pacemaker when he calls the arrhythmia "Interferenz-dissoziation."

and that he specifically chooses this term to differentiate the arrhythmia from atrioventricular block. (p. 266)

Die Durchleitung der vorzeitigen Schläge übt auf den Ort der automatischen Reizbildung (für die Kammer dieselbe Wirkung aus, als ob ei U sprungsreiz gerade von ihm bgegeben wäre die Reizbildung beginnt was die Länge der folgenden Kammerperiode zeigt, von neuem Der geleitete Reiz zerstört den sich bildenden Ursprungsreiz uber den er hinweggeht. An diesen Stellen erfolgt die Verkettung beider Rhythmen Here Mobitz describes entricular capture by the auricular node and observes that the passage of the sinus impulse discharges the atrioventricular pacemaker He uses the term "linkage (Verkettung) to describe this capture. (p.260) The use in the same paper of the phrase Interferenzdissoziation mit Verkettung les es no doubt that Mobitz intended the word "interference to refer to the effect of the discharge of the ectopic pacemaker and "Verkettung to describe sinus capture Marriott, in the article quoted elsewhere in this paper mistakenly gives Wenckebach and Winterberg credit for coining the phrase "linkage of rhythms. Actually Mobitz originated the phrase and the concept nd described the phenomenon t length in his remarkably perceptiv study

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Ventricular parasystole in atrial fibrillation

Parasystolic arrhythmias ha been commonly described in sinus rhythm with an independent entricular center stimulating some of the entricular beats. This type of arrhythmia has rarely been reported in trial fibrillation. The case reported in this communication demonstrates in atrial fibrillation the development of an independent entricular rh thm alternating th rregular beats of supra entricular origin (Fig 1, B and C).

A.S., 57 year-old man, was admitted to Mt. Sinai Hospital, Mi neapolis, Minn on Jan. 4 1962, and died on Feb. 4 1962. His complaints were orthopnea and nocturnal dyspnea. On previous admission in 1960 he was found to ha trial fibrillation and had been digitalized since that time Arteriosclerotic heart disease was considered to be the cause of the arrhythmia. On the final admission, the patient as found t be in respiratory distress. The blood pressure was 150/80 mm. Hg There were numerous bilateral basal râles. The heart was greatly enlarged, the rhythm was irregular and no murmurs were heard A chest x-ray film confirmed the finding of cardiac enlargement and also revealed vascular engorgement and pleural effusion bilaterally The blood urea nitrogen at the time of his admission to the hospital was 36 mg per cent, and it rose to 61 terminally Electrocardiograms showed trial fibrillation ith arying periods of sinus rhythm although no antifibrillatory drugs ere used The patient had been digitalized prior to admission, and digitoxin, 0.1 mg was continued daily

On Jan. 20, 1962, unusual electrocardiographic pattern developed (Fig 1 B and C). Atrial fibrillation was present throughout the record with the typical arrhythmia of the conducted (narrow) entricular beats. I addition, episodes of alternating wider (0.10 second) entricular complexes,

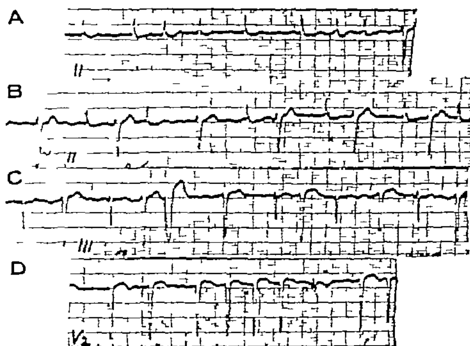


Fig. 1. A, Lead II Jan. 15, 1962 trial fibrillation. B, Lead II Jan. 20, 1962, regular ide rS w es alternating with irregular complexes identical to those in A. C, Jan. 20 1962, Lead III same rhythm w th one beat from another ventricular focus (fifth). D, Jan. 26, 1962, Le d V trial fibrillation w th one entricular complex.

of different ontour nd direction appeared I Lead II (Fig. 1,B) the complexes were bidirectional. The rhythm of these entricular complexes was nearly regular (arying from 0.84 to 0.90 second), ontrast t the irregularly spaced narrower con ducted QRS complexes. Also the interval between the narrow conducted and the wider QRS complexes was irregular (arying from 0.34 to 0.60 second), excluding entricular bigeminy due to fixed coupled premature entricular beats. The electrocardiogram therefore, shows transient co-existence of trial fibrillation nd an independent ventricular pacemaker. This type of arrhythmia is in principle interferenc dissociation of an ectopic trial pacemaker (trial fibrillation) and entricular pacemaker. It is irrelevant for this concept whether single or multiple auricular pacemakers are assumed. Furthermore, transient protecti A-V block must be assumed following the conducted beats as necessary condition for the existence of this or related types of arrhythmia. Usually the coexistence of egular sinus nodal, and entricular pacemakers are the basis for interference dissocia tion, but there is no reason why this concept should not pply to trial fibrillation. The arrhythmia as observed in this case has also relationship to the bidirectional tachycardia reported recently by Chevalier. However tachycardia was not present in our patient except in Lead V where it was not bidirectional. Chevalier in his survey of the l ter ture discusses the usually grave clinical condition of patients w th this type of arrhythmia. Our patient died 1 month after the tracings shown in Fig. 1 were recorded. Autopsy (limited t bdomen) showed far dvanced aortic arteriosclerosis.

Chevalier also calls attention t the possibility that overdigitalization may cause such arrhythmias. Therefore digitalis antagonists, such as potassium chloride may be of benefit. I our case, the digitalization had been continued ntil the episode of Jan. 20 1962. The arrhythmia under discussion was of short duration since the tracing recorded 5 days earlier showed only atrial fibrillation whereas that recorded 6 days later showed atrial fibrillation with occasional entricular extrasystoles.

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Book reviews

CARDIOVASCULAR ABSTRACTS (Selected from World Literature). Edited by Stanford Wessler M D Assistant Professor of Medicine, Harvard Medical School and Visiting Physician, Beth Israel Hospital, Boston Mass. (Associate Editor Circulation Editorial Assistant—Naomi Glazier). American Heart Association Monograph Abstracts II—1961 New York, 1962, American Heart Association Inc 191 pages. Price $2 75

This paper-bound volume is collection of abstracts from the international literature on cardiovascular disease and research. The paper betracted were selected mainly from those published in 1960 and 1961

It is a comprehensive selection organized according to heterogeneous categories, e.g "hypertension," pharmacology physiology physical signs, etc Most of the betracts are brief pertinent, and well written, summarizing the aims and results of the studies. Little attempt is made to reproduce the uthors discussions, but conclusions and hypotheses are sometimes m cluded. Of course the actual data are included ery briefly or not t all. Instances of over simplification nd misrepresentation, inherent in this type of eport, are minimized by the abstractors. It is recommended as con enient source of references and information

TOBACCO AND HEALTH Edited by George James M D Deputy Commissioner Department of Health Adjunct Associate Professor Public Health Practice, Columbia University School of Public Health nd Administrative Medicine, New York City and Theodore Rosenthal, M D Assista t Commissioner Department of Health Clinical Professor of Preventiv Medicine, New York University College of Medicine New York City Springfield, Ill. 1962 Charles C Thomas Publisher 408 pages. Price $13 75

Under the auspices of he New York Sta Academ of Preven ive Medicine nd the New York Academy of Medicine Symposium as held to search for the proof or lack of proof of the causal relationship of cigarette smoking t lung cancer The papers represent both sides of the controversy and are divided into four major groups namel (1) Chemistry and Pharmacology of Tobacco (2) The Experimental P thology of Tobacco Smoke (3) I terpreta ion of Statistical and Epidemiological Data Relat ng Smoking to Disease (4) Smoking and Lung C nc nd (5) Other Diseases Relating to Smoking

Tobacco smoke is complex mixtur of chemicals which are present either in the gas phase (carbon monoxide nd h drogen cy nide) or in the liquid aerosol or particulat phase (actively based on measurement of nicotine). The particulat phase of the smoke is impacted in the re spira ory tract and then either bsorbed or mechanically removed This hemical mixtur contains, by analytical in estiga ion 2?0 organic compounds and 15 elements as inorganic com pounds. These include 16 carcinogens. A great deal more analytical work is needed to ttain more precise knowledge of tobacco smoke. The difficulties are concerned w th the variable nature of the original material, tobacco and the many ariables of the smoking process.

A noticeable chemical difference between cigarette smoke nd cigar and pipe tobacco is demonstrated by the strongly acid nature of cigarette smoke and the basic character of cigar and pipe tobacco smoke. These differences are probably associated with the methods of curing of the various tobaccos as well as the differences i combustion temperature.

Therefore the first great difficulty in determining the effect of smoking on man is the complexity of the tobacco smoke The second difficulty is that man is the only animal who smokes oluntarily and this act of smoking cannot be d plicated in nimals.

The findings of numerou histopathological and epidemiological in estigations are consistent ith the theory that hea y cigarett smoking is an important factor in the causation of bronchogenic carcinoma nd mortality from t. On the other hand the opponents of these in estigations belie that the role of cigarett smoke in the pathogenesis of cancer may be due to differences between smokers nd nonsmokers in characteristics other than smoking or a wholl nonspecific effect of the smoke.

This book can be recommended because of the newer methods used and the comprehensiv discussions of *this* controversy It is usef l, stimulating nd thought-provoking book.

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASES. METHODOLOGY HYPE TENSION AND ARTERIOSCLEROSIS (Supplement to *American Journal f Public Health d the Nation Health* Vol. 50 N 10 October 1960). Report of Conference held t Princeton N J April 24-26, 1959 Guest editors Herbert Pollack, M D and Dean E. Krueger published jointly by the American Heart Association nd National Heart Instit te 124 pages. Price $1

I is very late to be publishing note on this report of the Princeton Conference, *nd for this* delay the reviewer is alone to blame. This report is so aluable document, however nd clinicians who may not already ha come across it are likely to find it so interesting that this review is better late than never The Conference Princeton held in April, 1959 brought together ma y of the leading epidemiologists of the United States and some from abroad, and goodly number of experts in the linical nd labor tory fields to help and advise The object of he meet ing was to continue the work tarted by the American Heart Association the National Heart Instit te, nd he World Health Organization in standardizing criteria and methods of stud of cardiovascular disease in population groups.

The problem may be illustrated quite simply How should the blood pressure be measured, or a history of angina taken so that results in field studies can be valid and informative and truly comparable from one study to another and from one continent to another The report deals successively with questions of design and analysis, and with clinical evaluation e.g what should be regarded as definite and what as possible infarct Methods are considered of assessing individual diet (in advanced societies dreadfully difficult problem to which there is yet no satisfactory solution), and habitual personal physical activity (to which likewise the epidemiologist has so far devoted himself). There are sections on body form and on biochemical problems There is rather long, but exceedingly interesting account of stress and social factors, the method of studying them and their possible relation to cardiovascular disease. Finally there is discussion of genetics.

Many comments might be made. For example the section on diet devotes too little attention to the question of fatty acids and that on physical activity although it is the most interesting account of the subject that the reviewer has read does not face up to the methodologic problems in applying scales in field studies of thousands of men However as reflection of current ideas and thinking on the tasks of epidemiology in cardiovascular disease the report is invaluable The editing is excellent.

BODY FLUID DISTURBANCES. From Symposium on Fluid Balance American Medical Association, 1961 Edited by W D Snively J M D New York, 1962 Grune & Stratton, Inc 122 pages. Price $4 75

This book represents the publication of papers given at an American Medical Association symposium in 1961 There are eight contributors, each responsible for chapter on selected aspect, and as might be expected this results in the field being covered somewhat patchily There are good sections on the basic principles of fluid and electrolytes in relation to clinical disturbances, dealt with in simple fashion, but specific recommendations for treatment are confined to the chapters on oliguria, pediatric problems, surgical patients, diabetes, and burns. One of the best chapters is that on the nutrition of the surgical patient. There is conspicuous paucity of advice on the management of medical problems of fluid and electrolytes in adults.

There are numbers of statements which the reviewer would not accept, such as mortality of 30 per cent in acute tubular necrosis in obstetric patients, even when optimally treated in the best centers, or that the ECG changes of hypokalemia in the course of diabetic coma are related to the potassium ion content of the cardiac muscle rather than to the extracellular fluid level.

This book will serve as easily readable introduction to the principles of the management of fluid and some aspects of their clinical application, and should be of value to general practitioners, or to medical students who cannot understand the more complicated standard text books on the subject.

ANTICOAGULANT THERAPY By A. S. Douglas, B. SC., M D F.R.F.P.S. F R.C.P (Ed.) M.R.C.P (Lond.), Senior Lecturer in Medicine University of Glasgow Honorary Consultant Physician Royal Infirmary Glasgow Scotland. Oxford, Blackwell Scientific Publications, 1962 394 pages. Price. 50 shillings. (U.S. F A. Davis Company Philadelphia. Price $9)

This comprehensive work adequately fulfills its objective, to give an up-to-date account of anticoagulant therapy It is directed primarily to the general physician and clinical pathologist, but also to others who carry part of the responsibility for the care of patients on such therapy The first 90 pages are devoted to a critical review of the present knowledge of the mechanism of thrombosis, the relative role played by platelets and by the blood coagulation and the changes in the constituents of the blood, in the blood flow and in the vascular wall which encourage thrombosis. These various themes are not developed in detail, but have been lucidly reviewed with regard to the different points and problems which are especially pertinent to the interesting discussion which follows on the action of anticoagulant drugs and the theoretical possibilities and limitations of this therapy The author correctly points out that anticoagulants in therapeutic dosage have little or no effect on the initial platelet thrombus formation. The main effect is to prevent the coagulation thrombus which most frequently causes vascular obliteration. These important introductory chapters are followed by informative descriptions of heparin and the coumarin drugs, their chemistry pharmacology and therapeutic characteristics. The author has succeeded extremely well in selecting essential data of importance for the application of these drugs in clinical practice.

The second half of the volume is reserved for comprehensive discussion on the therapeutic indications for anticoagulant therapy its management, and laboratory control. These controversial problems have been treated in an objective, critical and fair way The indications outlined are based on the best designed trials which have been published so far The description of the organization of anticoagulant therapy as an outpatient service is detailed and comprehensive and gives very useful practical advice for all those who are responsible for this therapy

The advantages and disadvantages of the different laboratory techniques are discussed. The author points out that, because of the use of the one-stage prothrombin test, the many different methods of expression of the results have led to great variation in intensity of therapeutic effect at different centers. Furthermore, the lack of standardization of the reagent between dif

ferent centers is a major disadvantage. H recommends either the P & P method or the Thrombotest method, which is centrally standardized and is simple to use

The rapid progress made within the field of blood coagulation and thromboses will ery soon provide data, in addition t those which were vailable to the author when the book was written, for a more thorough evaluation of the different laboratory techniques. Knowledge is rapidly increasing in regard t the behavior of the different clotting factors at arious stages of therapy and the relation between the concentration of individual clotting factors nd bleeding and thrombosis tendency The great importance of controlling factor X (Stuart Prower factor) has already been established and thromboplastins which provide good control of this factor therefore, should be preferred. Unfortunately some of the most widely used commercial thromboplastins are inadequate in this respect. These and other basic problems of importance for successful, safe, and efficient therapy will presumably be considered in the next edition. In most other respects, however this book will not likely be out of date in the near f ture.

It can be highly recommended, therefore, as source of very valuable information for all who are interested in anticoagulant therapy

PERIPHERAL VASCULAR DISEASES. Third edition, by Edgar V Allen, B.S Nelson W Barker B.A. and Edgar A. Hines, J B.S. with the assistance of John A. Spittell, J B.S., John F Fairbairn, II M.D and John L. Juergens, B.S all of the Section of Medicine, Mayo Clinic, University of Minnesota. Philadelphia, 1962, W B Saunders Company 1,044 pages. Price $18.

In the reviewer opinion, this book has been the best over-all vailable text on peripheral vascular disease for number of years. It is well known and holds a respected position among physicians and students. This third edition is certainly welcomed.

Most specialists in cardiovascular disease are quit familiar w th the contents of previous editions. Much of this informa ion is retained, of course, but modifications in consonance with progress in arious areas are readily apparen New or greatly mplified subject include circulatory physiology cerebral vascular disease ngiography and recent advances in blood coagulation and thrombosis.

This book can be highly recommended. My only reserv ion is tha It might be too extensi for immediat worth t the busy practi ioner or medical student This group probably would do better with more condensed presentation. Since most physicians do not expect to become experts I the field of peripheral vascular disease, there is natural reluctance on their part read an extensi text and even to keep abreast with the recent litera ure. Unfortunately in most medical centers, teaching nd training in vascular disease is poorly emphasized and relegated to secondary position. All of this is regrettable in light of an increasing geriatric population and the rapidly growing importance of peripheral vascular diseases.

It would be ideal if all internists, general practitioners and medical st dent could thoroughly digest a book such as this one nd pply this knowledge to their care of patients. Unfort nately this is impractical. Certainly however all cardiologists should be intimately familiar with the contents of this publication.

SURGERY OF THE CHEST Edited by John H Gibbon, Jr M D Samuel D Gross Professor of Surgery nd Chairman of the Department of Surgery The Jefferson Medical College. Philadelphia 1962, W B Saunders Company 902 pages. Price $27

This book is by far the most complete nd authorita ti olume a ailable on surgery of the chest. It represents the combined efforts of 33 authors and has been edited by John H Gibbon, J

The book itself is a commendable achievement. All phases of thoracic surgery including physiology roentgenology pathology and anesthesia are included, along with discussions of technical surgery Furthermore, there are several sections which deal with various aspects of cardiovascular surgery an area which has been expanded greatly since publication of previous textbooks of thoracic surgery

As in all texts which result from the work of multiple a thors, there is considerable variation in style overlapping of material, and a certain imbalance of contents. These however are not serious defects and do not seriously detract from the value of the book.

The book has been published in an ttractive style with generous illustrations, nd it is well indexed The editor authors, and publishers are to be congratulated and the book is recommended to all with an interest in surgery of the chest

EL SONDEO CARDIACO EN LAS CARDIOP TIAS ADQUIRI AS. By Gonzalo Sepulveda D Professor extraordinario de Medicina Jefe del Laboratorio Cardiopulmonar en el Centro de Cardiologia del Hospital Clinico Jose Joaquin Aguirre, Uni ersidad de Chile, Santiago, Chile Santiago, 1962, Centro de Publicaciones Biologicas, 226 pages.

This book is primarily intended to provide an elementary knowledge of the principles and practice of catheterization of the right side of the heart as pplied to the diagnosis and evaluation of acquired heart disease. The use of indicator-dilution techniques has been purposely omitted since it will be the subject of nother monograph, now in preparation. The thor first presents a careful description of the techniques and of the interpretation of data. This is followed by sections on pulmonary hypertension cor pulmonale, the hemodynamics of mitral stenosis, mitral

quantity of food previously consumed based on recollection might be questionable, the qualitative answers given were very uniform and revealed two outstanding differences between the food consumed in the Yemen and that in Israel. (1) In the Yemen the fats were mainly or solely of animal origin: Samne (dehydrated butter), milk, mutton, beef, and very few eggs; vegetable oil was very rarely used. In Israel the settled group consumed similar total amounts of animal fat together with margarine (40 to 50 Gm. daily) and in addition about 30 Gm. of vegetable oil (soya, sesame, and olive). (2) The carbohydrates consumed in the Yemen consisted solely or mainly of starches; almost no sugar was used. In Israel sucrose accounted for 25 to 30 per cent of the total carbohydrates. The above-mentioned differences hold true also when a comparison is made between the diet in the Yemen and the diet of the settlers of European origin.

Thus, neither the total saturated fat content of the diet nor the lack of unsaturated fat can explain the rareness of ischemic heart disease and diabetes in the recently immigrated Yemenites. The total caloric intake was a little less in the Yemen than in Israel, a fact that was reflected in the average body weight of the settled Yemenites, which was 9 kilograms more than that of the new immigrants. However, the diet in the Yemen was by no means a starvation or semistarvation diet, as has been attested by Dr. S. Nassan, who spent two summers with Yemenite Jews in the Yemen prior to their mass immigration to Israel.[7] Nor is the diet in Israel excessive. These observations, therefore, do not support the conclusions of other epidemiologic studies that high rates of ischemic heart disease are related to diets rich in saturated fats.

Diabetes and atherosclerosis are often related; atherosclerosis is twice as common in diabetic patients as it is in the general population. Both diseases increased in prevalence among Yemenite immigrants after they changed their environment. Although atherosclerosis is generally accompanied by disturbed lipid metabolism, the bearing of such disturbance on the pathogenic mechanism of atherosclerosis—whether it affects the deposition of lipids in the arterial wall, coagulation of blood, fibrinolysis, or is a mere chance association—is unknown.[9] Diabetes, especially if poorly controlled, is frequently accompanied by hypercholesterolemia and raised levels of triglycerides.[10,11] On the other hand, atherosclerosis is also associated with disturbed carbohydrate metabolism despite a normal fasting blood sugar.[12]

Obesity is a predisposing factor in the development of both atherosclerosis and diabetes. Lately, physical activity has been considered to be related to the development of atherosclerosis. Mortality from sudden coronary occlusion was found to be lower in heavy working than in light working groups,[13] although little difference was found in their dietary patterns.[14] Exercise is also known to improve the diabetic state and reduce the daily requirement of insulin.

Not only carbohydrate metabolism but also fat metabolism is dependent upon insulin,[15,16] and, in addition, deprivation of insulin inhibits the incorporation of amino acids into proteins and the synthesis of connective tissue mucopolysaccharides.[1] A greater amount of fibrillary highly polymerized mucopolysaccharides has been demonstrated in the aortas of diabetic patients than in nondiabetic patients. A significant change in the diet of Yemenites after their settlement in Israel is the increased consumption of sugar. A close relationship has been demonstrated between the ingestion of sucrose and the death rate from diabetes,[19] and a closer relationship has been found between the incidence of death from coronary disease and sugar in the diet, than any other nutrient in the diet.[20] When the intake of protein was kept constant, sucrose-fed animals gave a higher glycemic response to an oral or intravenous glucose load than did starch-fed animals, indicating that in the former the glucose load was not matched by a proper insulin response,[21,22] i.e., a relative insulin insufficiency. Furthermore, sucrose-fed animals have higher levels of plasma cholesterol and beta lipoproteins[23] and a greater amount of hepatic lipids than do starch-fed animals, but the proportion of

the linoleic acid in the lipids falls more rapidly with sucrose feeding than with starch feeding.[23,24]

The role of vascular wall damage in the pathogenesis of atherosclerosis has been increasingly stressed.[25,26] It is possible that excessive ingestion of sucrose leads to a state of "relative insulin insufficiency" which in turn causes impaired metabolism of the vascular structures, and disposes them to the infiltration of lipids. The fact that patients with mild diabetes may have atherosclerosis, whereas others with severe, long lasting uncontrolled diabetes may escape it, raises the possibility that some defect of the vascular system may be genetically transmitted and that in these individuals even a mild degree of insulin deficiency may be sufficient to initiate the onset of atherosclerosis.

If a nutrient is an etiological factor underlying the increased incidence of atherosclerosis and diabetes in Yemenites who have lived in Israel for many years, it seems that suspicion must fall on the ingestion of sucrose. The increased consumption of sucrose might, therefore also be responsible for the increased prevalence of these diseases in the general population. The observations outlined seem to warrant further epidemiologic and laboratory investigation.

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Clinical communications

Effect of long term treatment with hydrochlorothiazide on water and electrolytes of muscle in hypertensive subjects

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The mechanism by which the thiazide derivatives lower the blood pressure has not yet been elucidated, but it seems in some manner related to their diuretic and saluretic properties. This assumption is supported by the finding of a high content of water and sodium in the vessels,[1-3] muscle,[4-6] and red cells,[7] and the hypotensive effect of low-salt diets and mercurial diuretics in experimental[8] and human[9-11] hypertension. No detailed study has yet been performed on the changes in water and electrolytes of muscle under the influence of the thiazide derivatives which could throw some light on the mechanism of their hypotensive effect. With this purpose in mind the extracellular and intracellular distribution of water and electrolytes in muscle was studied in hypertensive subjects after prolonged treatment with hydrochlorothiazide (HCT).†

Material and methods

Five normal subjects and 8 hypertensive subjects were selected for study. Hypertension was asymptomatic, protracted, and of the benign type, without evidence of cardiac or renal failure. The patients were ambulatory and conspicuously free of edema and/or dyspnea. Blood urea and creatinine were normal in every case, and creatinine clearance ranged from 72 to 120 ml. per minute.

Biopsies of muscle and samples of blood were taken once, in the normal subjects, and twice, before and after treatment, in the hypertensive subjects. The treatment consisted in the daily administration of HCT, 50 mg. twice daily, during periods that ranged from 22 to 48 days. All the subjects were submitted to standard diets with the addition of 2 Gm. daily of sodium chloride.

Samples of muscle of 1 to 2 Gm. were taken from the deltoid muscle; small amounts of procaine were used to infiltrate the superficial planes. The tissue was quickly blotted on a filter paper to remove the excess blood and was then placed in a stoppered, wide mouthed flask and weighed. Afterward it was dried in a vacuum oven at 70°C. to constant weight.

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†Hydrochlorothiazide was kindly supplied by Lepetit Argentina.

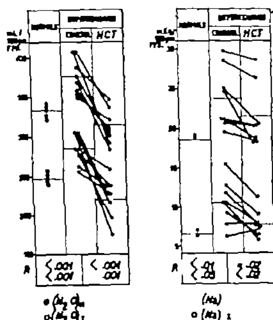


Fig. 1. Content of total muscle and intracellular water and sodium in normal and hypertensive subjects. Changes after hydrochlorothiazide therapy. $(H_2O)_M$ Total muscle water. $(H_2O)_I$ Intracellular water. $(Na)_M$ Total muscle sodium. $(Na)_I$ Intracellular sodium.

The fat was removed by successive washings with anhydrous ether and the weight of the dry fat free muscle was again recorded. This was used as a reference point for all subsequent determinations.

The dried muscle was digested with 0.75N nitric acid at 80° to 90° during 4 hours filtered through glass wool and made up with distilled water to a final volume of 10 to 25 ml. according to the initial size of the sample. In the final volume, sodium and potassium were determined by flame photometry and chloride by the potentiometric method of Sanderson.[13] Sodium and potassium in plasma were determined by flame photometry and chloride by Scribner's modification of the method of Schales and Schales.[14]

Calculations

Values expressed as contents per 100 Gm. of fat free solids (FFS) are given in parentheses ( ) and values expressed as concentrations per liter are given in brackets [ ].

Assuming that chloride in muscle is predominantly extracellular its volume of distribution (the "chloride space") was taken as a measure of extracellular water according to the equation

$$(H_2O)_E = \frac{(Cl)_M \times 0.90}{[Cl]_P} \times 1\,000 \quad (1)$$

where $(Cl)_M$ represents the chloride content of muscle in milliequivalents per 100 Gm. of FFS $[Cl]_P$ the plasma chloride concentration in milliequivalents per liter and 0.90 the combined correction for the plasma water (0.95) and the Gibbs-Donnan factor (1.05).

The content of intracellular water was calculated as

$$(H_2O)_I = (H_2O)_M - (H_2O)_E \quad (2)$$

The content of extracellular sodium was calculated as

$$(Na)_E = [Na]_P\,(H_2O)_E, \quad (3)$$

assuming that $[Na]_E$ equals $[Na]_P$ since in calculating cation concentrations the Gibbs-Donnan effect and the correction for serum water cancel each other.

The content of intracellular sodium was calculated as

$$(Na)_I = (Na)_M - (Na)_E \quad (4)$$

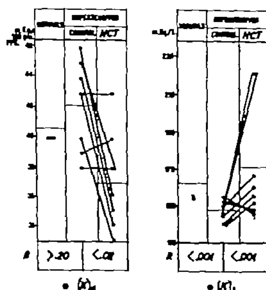


Fig. 2. Content of total muscle potassium and concentration of intracellular potassium in normal and hypertensive subjects. Changes after hydrochlorothiazide therapy. $(K)_M$ Content of total muscle potassium. $[K]_I$ Concentration of intracellular potassium.

Table I. Plasma electrolytes and water and electrolytes of muscle in normal subjects and in hypertensive patients before and after treatment with hydrochlorothiazide

Subject	Diagnosis	Stage	Plasma HCO (mEq./L.)	Plasma Cl (mEq./L.)	Plasma Na (mEq./L.)	Plasma K (mEq./L.)	Muscle $(H_2O)_M$ (ml./100 Gm. FFS)	Muscle $(H_2O)_E$ (ml./100 Gm. FFS)	Muscle $(H_2O)_I$ (ml./100 Gm. FFS)	Muscle $(Na)_M$ (mEq./100 Gm. FFS)	Muscle $(Na)_E$ (mEq./100 Gm. FFS)	Muscle $(Na)_I$ (mEq./100 Gm. FFS)	Muscle $(K)_M$ (mEq./100 Gm. FFS)	Muscle [Na] (mEq./L.)	Muscle [K] (mEq./L.)	$[Na]_E/[Na]_I$	$[K]_I/[K]$
N.S.	Normal	—	27	105	146	5.1	320	80	240	18.8	11.6	7.2	40	30	166	4.86	32.5
N.A.	Normal	—	28	108	142	5.0	342	86	256	21.1	12.1	9.0	40	35	156	4.04	31.2
R.F.	Normal	—	26	104	146	5.1	327	86	241	18.0	12.2	5.8	44	24	182	5.95	35.0
J.P.	Normal	—	27	108	147	4.2	332	80	252	16.7	11.7	5.0	39	20	154	7.42	36.2
F.C.	Normal	—	24	98	138	4.6	339	90	249	19.0	12.4	6.6	40	26	160	5.20	34.7
A.G.	Hypertensive	Control	29	106	143	4.7	387	101	286	20.5	14.3	6.2	39	22	141	6.62	30.6
		HCT	33	103	145	4.1	347	91	256	20.3	13.2	7.1	40	28	156	5.23	38.0
A.L.	Hypertensive	Control	29	107	145	5.0	359	73	286	21.1	10.7	10.4	44	36	153	3.98	30.6
		HCT	29	105	148	3.9	308	73	235	18.8	10.8	7.9	35	34	149	4.37	34.6
F.M.	Hypertensive	Control	27	109	147	5.0	352	91	261	21.1	13.4	7.7	38	29	145	5.07	29.0
		HCT	28	102	148	4.3	321	85	236	20.4	12.6	7.8	38	33	161	4.45	37.4
A.C.	Hypertensive	Control	29	111	146	4.6	376	70	306	19.3	10.2	9.1	43	30	140	4.91	30.4
		HCT	27	107	150	3.5	302	79	223	18.3	11.8	6.5	34	29	152	5.08	43.4
P.C.	Hypertensive	Control	—	104	145	4.8	353	96	257	24.4	14.0	10.4	40	40	155	3.58	32.2
		HCT	2	94	141	4.8	312	88	224	18.3	12.4	5.9	33	26	147	5.36	30.6
A.B.	Hypertensive	Control	32	111	146	4.2	369	90	279	24.8	13.7	11.7	43	42	154	3.48	36.6
		HCT	31	99	147	4.2	284	91	193	20.6	13.3	7.3	43	38	222	3.88	52.8
M.F.	Hypertensive	Control	26	110	146	5.8	407	101	306	29.7	14.5	15.3	45	50	147	2.94	25.3
		HCT	30	99	146	3.2	292	121	171	28.8	17.6	11.2	38	65	222	2.23	69.3
C.S.	Hypertensive	Control	25	105	149	5.2	407	104	303	28.3	15.6	12.7	46	42	151	3.55	29.0
		HCT	31	100	143	3.2	337	122	215	26.4	17.4	9.0	36	42	167	3.42	52.1

$(H_2O)_M$ = Content of total muscle water. $(H_2O)_E$ = Content of extracellular water. $(H_2O)_I$ = Content of intracellular water. $(Na)_M$ = Content of total muscle sodium. $(Na)_E$ = Content of extracellular sodium. $(Na)_I$ = Content of intracellular sodium. $(K)_M$ = Content of total muscle potassium. $[Na]_I$ = Concentration of intracellular sodium. $[K]_I$ = Concentration of intracellular potassium. FFS = Fat-free solids. HCT = Hydrochlorothiazide.

The content of extracellular potassium was not calculated because it represents a negligible fraction (about 0.5 mEq.) of total muscle potassium (K_M), the latter value being taken as equivalent to intracellular potassium.

From these values, concentrations of sodium and potassium in intracellular water were also derived.

The content values of water and electrolytes were expressed in milliliters and milliequivalents per 100 Gm. of FFS, respectively. Concentration values of electrolytes were expressed in milliequivalents per liter.

Results

The results are summarized in Tables I-IV and Figs. 1 and 2. Normal values agree with those found by other authors.[14]

Compared to the group of normal subjects the hypertensive subjects showed higher total muscle water ($p < .001$) and sodium ($p < .01$). Since extracellular water and sodium did not differ significantly from normal values ($p > .30$ and $= .10$), the excess of both were located in the intracellular space ($p < .001$ and $< .05$). *There was a tendency for sodium to be retained in excess of water, so that the concentration of sodium in intracel*

Table II. Statistical evaluation of water and electrolytes of muscle in normal subjects and in hypertensive patients

Subjects		$(H_2O)_M$ (ml./100 Gm. FFS)	$(H_2O)_E$	$(H_2O)_I$	$(Na)_M$ (mEq./100 Gm. FFS)	$(Na)_E$	$(Na)_I$	$(K)_M$	$[Na]_I$ (mEq./L.)	$[K]_I$	$[Na]_E/[Na]_I$	$[K]_I/[K]_E$
Normal	Mean	332	84.4	247	18.6	12.0	6.7	40.6	27.0	163	5.49	33.9
	SD	± 8.9	± 4.3	± 6.7	± 1.6	± 0.03	± 1.5	± 1.9	± 5.7	± 3.5	±1.2	± 2.0
	SE	± 4.4	± 1.9	± 3.3	± 0.8	± 0.01	± 0.6	± 0.9	± 2.6	± 1.6	±0.6	± 0.9
Hypertensive	Mean	376	90.7	285	23.6	13.3	10.4	42.2	36.3	148	4.26	30.5
	SD	±22.3	±12.9	±19.3	± 3.9	± 1.9	± 2.9	± 2.9	± 8.9	± 5.9	±1.2	± 3.2
	SE	± 7.9	± 4.6	± 6.8	± 1.4	± 0.7	± 1.0	± 1.0	± 3.2	± 2.1	±0.5	± 1.1
	p	<.001	.30	<.001	<.01	= .10	<.05	>.20	<.05	<.001	>.10	<.05

For meaning of symbols see Table I.

Table III. Statistical evaluation of the per cent changes in water and electrolytes of muscle in hypertensive subjects after treatment with chlorothiazide

Subjects	$(H_2O)_M$	$(H_2O)_E$	$(H_2O)_I$	$(Na)_M$	$(Na)_E$	$(Na)_I$	$(K)_M$	$[Na]_I$	$[K]_I$	$[Na]_E/[Na]_I$	$[K]_I/[K]_E$
A.G.	−10.3	− 9.9	−10.4	0.0	− 7.8	+14.5	+ 2.5	+27.2	+10.6	−20.9	+ 24.1
A.L.	−14.2	0.0	−18.1	−10.9	0.0	−24.0	−20.4	− 5.5	− 2.6	+ 9.7	+ 13.0
F.M.	− 8.8	− 6.5	− 9.6	− 3.3	− 6.0	+ 1.3	0.0	+13.7	+11.0	−12.2	+ 28.9
A.C.	−19.7	+11.5	−27.1	− 5.2	+13.5	−28.6	−20.9	− 3.3	+ 8.5	+ 3.4	+ 42.7
D.C.	−11.6	− 8.2	−12.8	−25.0	−11.4	−43.3	−17.5	−35.0	− 5.1	+49.7	− 4.9
A.B.	−23.0	+ 1.1	−30.8	−16.9	− 2.9	−37.6	0.0	− 9.5	+44.1	+11.4	+ 44.2
M.F.	−27.0	+16.0	−44.1	− 3.0	+17.4	−26.8	−15.5	+30.0	+51.0	−24.1	+173.9
C.S.	−17.2	+14.7	−29.0	− 6.7	+10.3	−29.0	−21.7	0.0	+10.5	− 3.6	+ 79.6
Mean	−16.5	+ 2.3	−22.7	− 8.9	+ 1.6	−21.6	−11.8	+ 2.2	+16.0	+ 1.7	+ 50.2
SD	± 6.4	±10.4	±11.3	± 8.5	±10.5	±19.6	±10.1	±21.2	±20.5	±23.4	± 33.9
SE	± 2.2	± 3.7	± 4.0	± 3.0	± 3.7	± 6.9	± 3.6	± 7.5	± 7.2	± 8.3	± 11.9
p	<.001	>.50	= .001	= .02	>.60	<.02	<.02	>.70	<.05	>.80	<.01

For meaning of symbols see Table I.

Table IV Changes in blood pressure and body weight in hypertensive subjects after treatment with hydrochlorothiazide

Subject	Days	Blood pressure (mm. Hg)						Body weight (Kg.)		
		Systolic			Diastolic			Control	HCT	Reduction (%)
		Control	HCT	Reduction (%)	Control	HCT	Reduction (%)			
V.G	22	230	160	30 4	125	95	24 0	82 0	80 0	2 4
A.L.	48	180	125	30 5	100	80	20 0	73 5	70 3	4 3
F M	43	200	155	22 5	120	95	20 8	56 3	55 1	2 1
A C.	35	240	175	27 0	140	110	21 4	94 0	92 5	1 5
D C.	41	180	135	25 0	120	95	20 8	66 3	65 5	1 2
A B	45	180	150	16 6	105	95	9 8	63 7	60 0	5 8
M F	37	180	160	11 1	105	105	0 0	81 5	76 8	5 7
C.S.	31	215	155	27 9	120	100	16 6	67 0	65 1	2 8
Mean	37 7	200 6	151 8	23 8	116 8	96 8	16 6	73 0	70 6	3 2

lular water was usually high ($p < .05$). Nevertheless because of the slightly higher concentration of sodium in serum the $[Na]_E/[Na]_I$ ratio did not differ significantly from that of normal subjects ($p > .10$). The potassium content of muscle was normal ($p > .20$) but because of internal dilution the concentration of potassium in intracellular water and the $[K]_I/[K]_E$ ratio were low ($p < .001$ and $< .05$).

The HCT elicited a decrease in total muscle water and sodium ($p < .001$ and $= .02$) which came out from the intracellular space ($p = .001$ and $< .02$). Correlations between losses of intracellular water and losses of sodium or potassium were poor ($r = 0.49$ and 0.35) and without statistical significance ($p > .20$ and $> .30$). The concentration of sodium in intracellular water and the $[Na]_E/[Na]_I$ ratio did not change significantly ($p > .70$ and $> .80$). Although the content of muscle potassium fell ($p < .02$) the decrease in intracellular water brought about an increase in the concentration of potassium in the latter ($p < .05$). This factor coupled to a decrease in plasma potassium elicited a very significant increase in the $[K]_I/[K]_E$ ratio ($p < .01$). Changes in extracellular sodium and water were erratic and without statistical significance ($p > .50$ and $> .60$). Changes in plasma included a tendency to hypochloremic alkalosis with hypokalemia without significant changes in sodium.

Blood pressure decreased from 11 1 to 30 5 per cent systolic and from 0 0 to 24 0 per cent diastolic. Body weight decreased from 1 2 to 5 8 per cent.

Discussion

Our finding of an increased content of water and sodium in muscle in hypertensive subjects is in accordance with the data of other authors in human[4] and experimental[5,6] hypertension. The results of tissue analysis do not agree in this respect with the measurements performed in the total body. Exchangeable Na^{24} although reportedly high in experimental hypertension has been found to be consistently normal in human hypertension.[13-15] These discrepancies may be due to the inadequacy of the body weight as a reference point because of the higher content of fat in experimental[6] or human[7] hypertension. In a later study[11] the exchangeable Na^{24} was found to be high when referred to the lean body mass.

The excess of sodium and water in muscle appears to be confined to the intracellular fluid since the chloride space did not differ significantly from that in normal subjects. This, along with the usual clinical signs, seems to rule out edema of cardiac origin. These data contra

dict the results of tissue analysis in experimental hypertension[6] and the measurements of the inulin and radiosulfate space in human hypertension,[22,23] since high values of extracellular fluid were obtained with both methods. However, the latter results have not been confirmed.[24,25]

The conclusion that the excess sodium and water in muscle belongs to the intracellular fluid is supported by the finding of d'Amico, Losse and associates, and Gessler[8] of a high content of sodium and water in the red cells in human hypertension.

The high concentration of sodium in intracellular water which was found by us has also been postulated by Ross.[19] This author simultaneously measured the exchangeable Na[24], the total body water (antipyrine), the serum sodium, and the extracellular fluid (thiosulfate) and from these data calculated the fraction of exchangeable Na[24] located outside the extracellular fluid which comprises the intracellular sodium and the sodium of bone. The concentration of this fraction per liter of water was found to be significantly increased in hypertensive subjects.

High concentration of sodium within the red cells has likewise been reported by d'Amico,[7] Losse and associates, and Gessler.

The potassium content of muscle also did not differ significantly from that of the normal group, a finding opposed to the data reported in experimental hypertension[6] but in agreement with the data in human hypertension. On the contrary, the intracellular concentration of potassium was low because of internal dilution, and since serum potassium concentration was normal, the ratio $[K]_I/[K]_E$ was also low.

It seems fair to assume that the decrease in total muscle water brought about by HCT occurred at the expense of intracellular water since the chloride space changed erratically and without statistical significance. This establishes a net difference with the effect of diuretics on edema of cardiac origin since in the latter instance the decrease in water and sodium come both from the intracellular and extracellular space as well, the latter being previously expanded. Our finding wholly confirms the results of Lawyers and Conway,[26] who found a decrease in total body water (antipyrine) without a change in the extracellular water (Na[24] space) after prolonged treatment with chlorothiazide. From these data the authors conclude that the water lost proceeded from the intracellular space. Similarly, Gessler[8] reported a decrease in the water content of red cells after treatment with Hygroton, a thiazide derivative. All these results contradict previous findings of Wilson[27] and Macleod and associates[9] who reported a decrease in extracellular water after a short term of chlorothiazide. The discrepancies might depend on the duration of treatment, since this effect was not observed by Cottier[13] and Wilkins and associates[16] after 4 to 8 weeks of treatment. Nevertheless, after the same duration of treatment a decrease in extracellular water was observed by Wilson and Freis[14] and by Winer.[12]

Since a fall in intracellular water did not correlate well with a fall in intracellular sodium and potassium, the former seems to be an independent phenomenon. However, magnesium of muscle has not been determined, so that one cannot conclude that the loss of intracellular water was not secondary to the loss of osmotically active particles.

The decrease in total muscle and intracellular sodium is supported by the finding of Winer[28] who reported a decrease in exchangeable Na after chlorothiazide, but the latter result has not been confirmed by Lawyers and Conway,[26] Wilkins and associates,[16] and Gifford and associates,[31] in spite of a negative sodium balance.[31]

The discrepancies between exchangeable Na[24] and sodium balance have been reported previously[14,32] and were ascribed to variations in the sodium of bone available for exchange.[33]

The decreased content of muscle potassium brought about by the drug confirms the data of Winer[28,12] who found a decrease in exchangeable K[42]. However, these findings do not agree with the data of Gifford[31] who found only a temporary decrease in exchangeable K[42] followed by normalization. Wilkins[16] also reported no change in exchangeable K[42] after chlorothiazide but, nevertheless, his data support the assumption that the thiazide derivatives do produce a moderate de

Table IV. Changes in blood pressure and body weight in hypertensive subjects after treatment with hydrochlorothiazide

Subject	Days	Blood pressure (mm. Hg)						Body weight (Kg.)		
		Systolic			Diastolic					
		Control	HCT	Reduction (%)	Control	HCT	Reduction (%)	Control	HCT	Reduction (%)
A.G.	22	230	160	30.4	125	95	24.0	82.0	80.0	2.4
A.L.	48	180	125	30.5	100	80	20.0	73.5	70.3	4.3
F.M.	43	200	155	22.5	120	95	20.8	56.3	55.1	2.1
A.C.	35	240	175	27.0	140	110	21.4	94.0	92.5	1.5
D.C.	41	180	135	25.0	120	95	20.8	66.3	65.5	1.2
A.B.	45	180	150	16.6	105	95	9.8	63.7	60.0	5.8
M.F.	37	180	160	11.1	105	105	0.0	81.5	76.8	5.7
C.S.	31	215	155	27.9	120	100	16.6	67.0	65.1	2.8
Mean	37.7	200.6	151.8	23.8	116.8	96.8	16.6	73.0	70.6	3.2

lular water was usually high ($p < .05$). Nevertheless, because of the slightly higher concentration of sodium in serum the $[Na]_E/[Na]_I$ ratio did not differ significantly from that of normal subjects ($p > .10$). The potassium content of muscle was normal ($p > .20$) but, because of internal dilution the concentration of potassium in intracellular water and the $[K]_I/[K]_E$ ratio were low ($p < .001$ and $< .05$).

The HCT elicited a decrease in total muscle water and sodium ($p < .001$ and $= .02$) which came out from the intracellular space ($p = .001$ and $< .02$). Correlations between losses of intracellular water and losses of sodium or potassium were poor ($r = 0.49$ and 0.35) and without statistical significance ($p > .20$ and $> .30$). The concentration of sodium in intracellular water and the $[Na]_E/[Na]_I$ ratio did not change significantly ($p > .70$ and $> .80$). Although the content of muscle potassium fell ($p < .02$) the decrease in intracellular water brought about an increase in the concentration of potassium in the latter ($p < .05$). This factor coupled to a decrease in plasma potassium elicited a very significant increase in the $[K]_I/[K]_E$ ratio ($p < .01$). Changes in extracellular sodium and water were erratic and without statistical significance ($p > .50$ and $> .60$). Changes in plasma included a tendency to hypochloremic alkalosis with hypokalemia without significant changes in sodium.

Blood pressure decreased from 11.1 to 30.5 per cent systolic and from 0.0 to 24.0 per cent diastolic. Body weight decreased from 1.2 to 5.8 per cent.

Discussion

Our finding of an increased content of water and sodium in muscle in hypertensive subjects is in accordance with the data of other authors in human and experimental[6] hypertension. The results of tissue analysis do not agree in this respect with the measurements performed in the total body. Exchangeable Na^{24} although reportedly high in experimental hypertension[7] has been found to be consistently normal in human hypertension.[8-10] These discrepancies may be due to the inadequacy of the body weight as a reference point because of the higher content of fat in experimental or human[10] hypertension. In a later study[11] the exchangeable Na^{24} was found to be high when referred to the lean body mass.

The excess of sodium and water in muscle appears to be confined to the intracellular fluid since the chloride space[17] did not differ significantly from that in normal subjects. This, along with the usual clinical signs, seems to rule out edema of cardiac origin. These data contra

intracellular water and sodium and higher concentrations of intracellular sodium Content of total muscle potassium was normal but, because of internal dilution the concentration of intracellular potassium and the $[K]_i/[K]_s$ ratio were low

HCT brought about a decrease in the content of total muscle and intracellular water sodium and potassium. The concentration of intracellular sodium and the $[Na]_s/[Na]_i$ ratio did not change significantly but the concentration of intracellular potassium and the $[K]_i/[K]_s$ ratio both increased

The possible bearing of these findings on the hypotensive effects of the drug are discussed

Addendum

After the completion of this paper a short abstract by Tobian and associates[18] came to our attention These authors report in rats a decrease in the intracellular potassium of muscle and in this sense their findings agree with ours. Nevertheless, no change in intracellular water and an increase in intracellular sodium were also reported which constitutes a fundamental disagreement with our findings. The reason for these discrepancies does not seem to be apparent and could be ascribed to differences in animal behavior and to the fact that the rats used were probably not hypertensive.

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Influence of rate of cuff inflation and deflation on observed blood pressure by sphygmomanometry

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The technique of inflation and deflation of the blood pressure cuff is subject to wide personal variation among physicians. It was thought that this may be one source of observer error noted by other workers,[1-4] especially since smaller errors are recorded by those workers using a double head-piece stethoscope[5] or a common manometer for two cuffs.

That no previous work has been done on this topic is probably due to the technical difficulty in precisely controlling the rates of change in pressure. As a cuff is inflated initially a large volume of air is required to fill out the wrinkles, the pressure then rises steeply to fall off later as the air compresses in the cuff. A variable change in the volume of the cuff depends on the displacement of flesh from under it. These factors can be precisely controlled only by a servo system.

In the servo system developed for this work the rate of change in pressure is converted by a metal bellows to a linear movement which can be compared to the movement of a nut on a screw thread driven by a constant speed motor. Any difference in the two movements actuates a rheostat to speed or slow an electric pump which inflates or deflates the cuff. Since the rate of compression of the bellows is continually matched to the movement of the nut, this latter factor can be used to predetermine the rate of change in pressure. The principle of the servo is shown in Fig. 1 and the complete apparatus is seen in Fig. 2.

The gearbox on the constant speed motor (a kymograph motor) gave pressure change rates of 2.35, 4.7, or 9.5 mm. Hg per second. The apparatus has an upper limit of 260 mm. Hg and worked satisfactorily

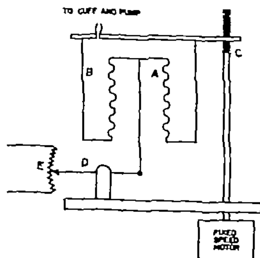


Fig. 1. Diagram showing principle of apparatus. A change in pressure in the cuff produces shortening of the metal bellows, A, contained in the chamber B. This chamber is moved in the opposite direction by the screw, C. Any differences in the o rates is reflected in the lever D which actuates the potentiometer E, t speed or slow the electric pump hich inflates or exhausts the cuff.

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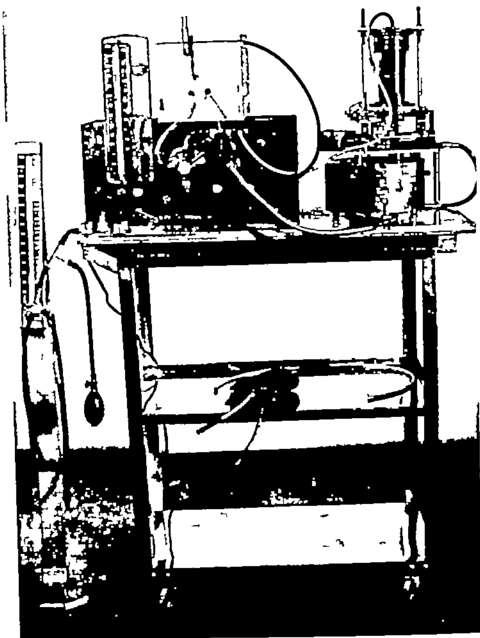


Fig. 2. The servo unit is mounted on the kymograph motor at the right. The motor driven pump in a soundproof box is on top of the electronic speed control unit. Separate manometers for the servo system and for the cuff are necessary when the cuff is inflated by hand.

except that, occasionally, feedback oscillations would occur when large arterial pulses were transmitted to the cuff particularly in obese subjects.

Fifty-five subjects were unselected except that all were in normal sinus rhythm and had systolic pressures of less than 260 mm. Hg. An 11-cm. cuff applied according to the American Heart Association recommendations, was not disturbed for the series of readings on each patient. The diastolic reading was taken at the silent end point. Each patient first had a casual blood pressure measurement, the cuff being inflated and deflated by hand. A further series of six readings was made by inflating the cuff by hand as rapidly as possible, at 9.5 or 4.7 mm. per second and

Table I Incidence of auscultatory gaps and occasions when no Korotkoff sounds could be heard with each method of inflating and deflating the cuff

Method *Inflate* *Deflate* (mm./sec.)	*By hand* *4.7*	*By hand* *2.35*	*9.5* *4.7*	*9.5* *2.35*	*4.7* *4.7*	*4.7* *2.35*
Auscultatory gaps	0	1	1	1	2	2
Sounds not heard	0	0	0	0	3	1

Table II Mean values of recorded blood pressure using different rates of inflating and deflating cuff

Method *Inflation* *Deflation* (mm./sec.)	*Casual**	*By hand* *4.7*	*By hand* *2.35*	*9.5* *4.7*	*9.5* *2.35*	*4.7* *4.7*	*4.7* *2.35*	
Systolic								
Mean value	140.2	132.2	134.8	132.5	136.5	132.5	133.7	Over-all mean 134.6
Deviation from over-all mean	+5.6	−2.4	+0.2	−2.1	+1.9	−2.1	−0.9	
Diastolic								
Mean Value	82.4	85.5	85.6	84.8	87.9	85.3	85.7	85.2
Deviation from over-all mean	−2.8	+0.3	+0.4	−0.4	+2.7	−0.1	+0.5	

Analyses of variance.

Systolic pressure
Subject variance = 234.7
Method variance = 7.9
Other = 30.0

Diastolic pressure
Subject variance = 383.0
Method variance = 6.1
Other = 41.0

Table III Mean values of recorded blood pressure presented in order irrespective of method of inflation and deflation of cuff

Order of presentation	*Casual*	*2*	*3*	*4*	*5*	*6*	*7*	*Over-all mean*
Systolic								
Mean value	140.2	137.2	135.9	133.3	133.0	131.5	131.4	134.6
Deviation from over-all mean	+5.6	+2.6	+1.3	−1.3	−1.6	−3.1	−3.2	
Diastolic								
Mean value	82.4	84.3	84.7	85.5	86.5	86.7	86.9	85.2
Deviation from over-all mean	−2.8	−0.9	−0.5	+0.3	+1.0	+1.5	+1.7	

Analysis of variance

Systolic pressure
Subject variance = 235.4
Time variance = 13.8
Other = 25

Diastolic pressure
Subject variance = 382.3
Time variance = 1.6
Other = 46

deflating at 4.7 or 2.35 mm. per second, the order of method being predetermined by random number tables.

The Korotkoff sounds tended to be of less intensity when the cuff was inflated and deflated at the slower rates and occasionally were inaudible. It appeared that auscultatory gaps were related to the intensity of Korotkoff sounds, the sounds temporarily faded below auditory threshold in the gap. These findings are in agreement with those of Rodbard and Margolis, although in this series age was not related to the incidence of auscultatory gaps. It has been shown that venous congestion induced by obstruction of the venous return and augmented by maintaining the cuff between systolic and diastolic levels[11, 12] attenuates the intensity of Korotkoff sounds.[9, 10] These mechanisms explain the increased frequency of auscultatory gaps and obliteration of the sounds at the slower rates of inflation and deflation (Table I).

Complete series of readings were obtained from 51 patients and submitted to statistical analysis. Evaluation of readings using each method (Table II) shows an error that would be expected from the difficulty of relating an intermittent sound to a continuously moving column of mercury. The observed pressure is lower when the column descends faster. The prediction that at normal heart rates the error will be a little less than half the travel of the column of mercury in 1 second[13, 14] is borne out by the systolic readings. That the prediction does not hold with the diastolic readings may be due to the feedback oscillations mentioned earlier. Analysis of variance showed that the variance due to the different methods of inflation and deflation was small.

The marked deviation of the casual readings is the result of variation in blood pressure with time. Evaluation of this factor is given in Table III, showing a progressive fall in systolic and a minor rise in diastolic pressures within the 15 to 20-minute period during which the measurements were taken. Analysis showed the time variance to be nonsignificant. The large residual variance unexplained by the controlled factors points to the need for further work on the accuracy of indirect measurement of blood pressure.

The conclusions from this work are that deflation of the cuff should be as slow as possible as the end points are passed. The rate of deflation at other times, and the rate of inflation have no significant effect on the observed blood pressure. Cuff pressure should not be held between systolic and diastolic pressure levels for longer than is necessary, since this may induce venous congestion distal to the cuff, causing attenuation of the Korotkoff sounds.

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This was found to be the case since unipolar records taken with the two types of instrument occasionally showed differences apart from those attributable to the differences in frequency response. For this reason only bipolar leads were used for the amplitude-response comparisons in this part of the study

Results Measurements were made of QRS amplitudes and durations in bipolar leads. Differences in QRS duration using the two types of instrument were minor and never exceeded 0 02 second A paper speed of 25 mm per second renders measurements of time intervals smaller than this very difficult. Nevertheless, a detectable apparent shortening of the duration of the direct writer QRS complexes occurred in 44 out of a total of 150 measurements.

Differences in QRS amplitude on the other hand were sometimes considerable. In each case in which a difference existed the direct writer amplitude was less than that observed with the Twin Beam The frequency distribution of the differences is shown in Table I In 150 measurements 81 per cent showed QRS amplitude differences greater than 0 1 mv 39 per cent showed differences of 0 2 mv or more and differences of 0 3 mv or more appeared in 12 per cent.

Study of the wave forms which showed the greatest attenuation revealed that peaked complexes suffered most, and in all cases in which there was minimal or no attenuation the complexes were rounded This is to be expected because the stylus must be given sufficient time to achieve its maximum displacement. Thus, it was often possible to tell which complexes recorded by the Twin Beam would be severely reduced but unfortunately one could not do this in reverse, i.e. it was impossible to tell from the appearance of complexes recorded by the direct writers whether curtailment had occurred Because different parts of a given QRS complex may have different degrees of peaking (for example the R wave may be rounded and the S wave pointed or vice versa) it might be expected that the R:S ratio could be seriously disturbed by the direct writer This was confirmed and in one case the ratio was changed from 0.8 to 0 4

Conclusion The above-described approach although technically simple suffered from two rather serious faults. In the first place comparisons of QRS amplitudes in tracings not simultaneously recorded are open to criticism because of the natural variation from beat to beat. Although it is possible to arrive at a reasonable average when a great number of complexes are recorded a certain degree of ambiguity between the comparisons remains. The second objection to the method is the impracticability of testing a great number of instruments upon one patient. But the results obtained with this first approach made it clear that significant errors in the measurement of QRS amplitude might derive from the use of direct writing electrocardiographs, although it was believed that considerable refinements in technique were required both to determine the extent of this error and to relate it to the frequency response of the instrument

Second approach

Method Precordial electrocardiograms were recorded on a D C magnetic tape recorder at positions V and V in 21 normal children The ages of the children ranged from 3 to 12 years. Precordial leads from children were chosen because it was believed that these imposed the most severe high-frequency requirements. The selection of chest leads was also influenced by the importance given to their QRS amplitudes in the diagnosis of ventricular hypertrophy On the magnetic tape the ECG signals were followed by a reference calibration signal and a series of sine waves that varied in frequency from 200 to 0 1 c.p.s The recordings were then played back through an attenuator into various direct writers, and the tracings were compared with a control obtained from a Twin Beam recorder To avoid nonlinearity at large deflections, signal levels were adjusted so that the lateral 0.5 cm of grid lines on the ECG paper were not used.

The over-all frequency response for the magnetic tape–Twin Beam system extended to 300 c p.s.

PROCEDURE FOR INSTRUMENT ADJUSTMENT A problem that arises in the testing of a hot-stylus direct writing electrocardiograph is that there are many factors which affect its response to high frequencies (30 c.p.s.

$$E = \frac{\text{QRS voltage indicated by Control} - \text{QRS voltage indicated by direct writer}}{\text{QRS voltage indicated by direct writer}} \times 100\%$$

$$= \frac{\frac{BT}{A} - \frac{bt}{a}}{\frac{bt}{a}} \times 100\% = \left(\frac{aBT}{Abt} - 1\right) \times 100\%$$

and above) Some of these factors are as follows (1) Stylus pressure This is used in some instruments to control damping by adjusting the stylus pressure or bending the stylus until a satisfactory square calibration signal is produced (2) Stylus temperature On some electrocardiographs, variations in stylus temperature produce a considerable change both in the shape of the one millivolt calibration signal and in the response to higher frequencies. (3) Build-up of wax underneath the stylus This limits the frequency response particularly at low stylus temperatures. (4) Build up of wax and particles of paper on the writer bar over which the paper passes beneath the stylus. (5) Paper tension The paper tension is sometimes affected by the size of the roll of supply paper in the instrument It affects the sharpness of the edge of the paper passing over the writing bar and thus affects the amount of friction the pen exerts on the paper and thus, the frequency response. (6) The output tubes and the setting of various internal controls in the instrument.

With all these factors affecting the frequency response of direct writers it might be expected that manufacturers specifications obtained presumably under laboratory conditions, would not always be met. On the other hand, our concern was with instruments as they are normally used The only assurance of a good response which operators of electrocardiographs normally have is the square appearance of the calibration signal. Preparation of the instruments prior to testing was limited, therefore to adjusting the stylus to give a clear line and setting the stylus pressure on the paper to give a satisfactory calibration signal. The calibration signal was considered to be satisfactory when it showed minimum slurring and minimum overshoot. Because the instruments were either new or were regularly serviced by the manufacturers representatives, we felt justified in taking the internal adjustments and tube complement as being satisfactory

A setting of stylus temperature control that would normally be employed by hospital technicians was adopted, although in general this is slightly lower than that which gives the best frequency response. It should be noted that the stylus temperature is affected by the speed of the stylus over the surface of the paper and will depend therefore to some extent upon what has just been inscribed. This means that there will be differences in stylus temperature variations when recording electrocardiograms and when recording sine waves.

The formula used for the percentage error E, in amplitudes of QRS complexes is shown at the top of the page. In the formula, A and a are the amplitudes (in millimeters) of the responses to calibration signals B and b are the amplitudes (in millimeters) of the responses to a particular tape-recorded QRS complex (upper-case letters apply to the control instrument, the Twin Beam and lower-case letters apply to the direct writer under test) and T and t are respectively the levels in millivolts of the calibration signal from the tape recorder as it appeared at the electrocardiograph input, and of the internal calibration signal of the direct writer To find the total error of a given instrument, t is taken at its nominal value of 1 mv i.e. no allowance is made for any error in the internal calibration signal. When a correlation between error and frequency response was looked for (*see below*) effects due to inaccuracy of the internal calibration signal were removed by replacing t with T

The value of T was determined by comparing it with a signal from a standard cell and potentiometer The error in this measurement did not exceed 1 per cent. The

measurements A a, B and b were made accurate to 0 1 mm by means of a vernier scale and magnifier The upper and lower bounds of all measurements are indicated by the suffixes $_+$ and $_-$ respectively the absence of a suffix indicates the actual measured value. In the most unfavorable cases, in which the uncertainties in all measurements displace the result maximally and in the same direction the over all accuracy in the determination of E will be approximately 5 per cent for QRS amplitudes of the order of 1 mv This means that if our results based on single measured values indicate that a particular instrument has an error in response to a particular QRS complex of 15 per cent its actual *error may be anywhere between 10 and* 20 per cent. To avoid unfairness in any particular case our results were interpreted in the manner most favorable to the instruments tested This entailed use of the upper or lower bounds for the abovementioned quantities, the choice being indicated by the formula.

In this analysis three distinct questions were asked (1) What is the greatest error shown by any instrument with respect to any QRS signal? (2) What is the response of an electrocardiograph to the whole set of 42 signal ? (3) How do the errors of the instruments correlate with their frequency response characteristics? For positive errors, the quantities A_+ B T a_- b_+, and t = 1 were used to obtain the most conservative possible answer to Question (1) so that we could be sure of an error *at least equal to E*. Because positive errors predominate, the value T_- was used throughout. Question (2) involves a generalization based on what may be thought of as 42 separate experiments in which there were 42 measurements B and b so that the quantities A_+ B T a_-, b and t = 1 were used Question (3) involves a generalization for each instrument over the 42 electrocardiograms, and a generalization of the effects observed in the 18 instruments, and therefore, requires removal of the internal calibration signal as a source of error For these reasons the quantities A_+, B T a, b and t = T were used.

*It may be noticed that errors are ex*pressed as a percentage of the indicated direct writing electrocardiograph signal rather than as a percentage of the control The reason for representing errors in this manner was that we wished to obtain figures for error referable to the tracings normally seen It may be observed that reliance is not placed upon the accuracy of the internal calibration signal of the Twin Beam control.

Results A comparison between 18 direct writers, produced by 5 different manufacturers, and the Twin Beam recorder on the basis of QRS amplitude differences in the reproduction of tape-recorded ECG signals is shown in Table II On the most conservative basis, amplitude differences

Table II *Reduction in QRS amplitudes in precordial-lead signals on magnetic tape when played back on direct writers*

Amplitude difference from control (mv)*	*Number of measurements*	*Percentage of total of 756 measurements*	*Percentage of total showing differences greater than upper limits of figures in left-hand column*
0 00-0 09	250	33	70
0 10-0 19	297	39	28
0 20-0 29	128	17	11
0 30-0 39	65	9	2
0 40-0 49	15	2	0 1
0 50 and over	1	0 1	
	756		

*Twin-Beam photographic recorder.

Table III QRS amplitude errors in 42 tape-recorded electrocardiograms reproduced by 18 direct

ECG	QRS amplitude in Tektronix model	6471	[illegible]	AK D[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Truman V	1.02 mv	3.8%	7.3%	3.3%	4.8%	2.1%	0.7%	7.3%	7.9%	8.0%
Trudie V	2.21	3.8	0.5	3.8	8.0	−0.8	11.8	10.7	11.7	16.8(17.0)
Leo V	1.65	6.8	2.4	7.0	0.0	0.2	11.8	10.1	10.7	13.0
Leo V	2.06	6.7	2.6	8.8	8.7	−0.0	0.3	10.7	11.0	14.1(14.1)
Nancy V	1.67	8.4	10.9	10.7	8.8	17.1(18.8)	12.8	9.9	13.6	18.1(18.0)
Nancy V	3.11	1.8	3.6	2.8	2.6	−4.9	3.5	3.1	3.6	0.1
Dean V	1.63	4.4	6.0	7.2	2.5	0.1	10.1	3.0	8.5	10.7
Dean V	2.19	1.0	−5.1	0.4	3.3	−11.3	4.1	5.0	2.0	5.8
Mary V	2.06	1.7	3.8	2.7	2.3	−3.6	6.0	7.4	8.7	0.2
Mary V	1.44	11.0	13.0	10.9(14.2)	15.3(14.7)	16.7(18.0)	21.6(18.0)	18.4(16.7)	16.7(18.0)	22.0(21.0)
Ann V	2.30	1.2	3.4	3.4	1.8	1.5	4.2	8.8	4.8	5.4
Ann V	2.00	2.8	0.8	2.3	4.0	−4.9	6.1	7.1	3.5	0.6
Allison V	1.93	1.4	1.3	1.7	3.3	1.9	3.0	5.4	8.7	1.9
Allison V	2.34	0.7	0.0	2.8	6.0	2.5	8.0	6.1	4.2	8.6
Kim V	2.07	5.3	4.3	7.8	4.7	0.3	7.8	6.1	8.4	8.0
Kim V	1.26	7.9	4.0	10.8	16.8(14.0)	13.8	15.6(13.7)	11.0	13.0	19.1(16.5)
John V	1.35	8.5	3.0	6.0	6.6	1.9	9.7	11.5	11.0	13.0
John V	1.91	2.3	−0.3	5.1	6.2	−4.8	7.3	8.4	9.0	11.1
Geoffrey V	1.14	7.3	13.0	8.3	0.2	4.1	0.5	13.0	10.4	13.5
Geoffrey V	1.89	1.3	4.0	0.7	3.0	3.3	3.3	4.8	4.0	6.7
Pat V	2.16	0.4	2.3	1.8	1.0	−2.7	3.3	5.4	4.0	4.0
Pat V	2.05	2.8	1.0	3.6	8.8	−3.1	8.4	0.7	10.2	11.0
Roger V	1.49	6.3	8.4	8.5	8.0	7.4	10.5	11.0	10.4	13.0
Roger V	1.30	5.8	0.8	7.4	10.8	0.3	12.3	11.8	12.0	11.7
Linda V	1.37	1.7	5.1	4.8	−0.9	3.0	6.8	6.0	6.8	8.0
Linda V	1.18	3.0	13.0	12.6	16.8	8.6	11.0	12.9	9.0	10.0
David V	2.15	4.0	−0.5	1.1	0.5	−0.3	3.2	5.2	5.1	2.3
David V	2.31	3.3	−5.3	3.3	−0.3	−14.0	−0.2	2.1	−0.7	−3.1
Shelley V	1.05	6.6	10.6(14.0)	5.8	1.0	3.3	0.1	12.3	0.3	9.6
Shelley V	0.90	31.6(28.1)	30.6(25.0)	34.0(31.0)	33.0(30.0)	31.7(18.0)	26.0(23.0)	36.4(33.0)	32.0(28.0)	[illegible]
Peggy V	1.36	2.3	6.3	2.8	3.9	−0.8	7.3	6.4	0.2	2.6
Peggy V	3.10	7.0	8.0	11.1	10.1	10.0	13.3	11.2	14.4	0.3
Patricia V	1.78	1.1	0.0	4.1	8.1	1.3	6.4	8.1	8.3	6.1
Patricia V	1.19	7.9	8.8	6.9	8.0	1.3	7.8	11.1	9.1	7.3
Myron V	3.27	1.2	2.0	1.3	1.7	−4.0	3.0	6.2	4.7	3.3
Myron V	2.81	1.3	−0.1	0.5	3.3	1.0	1.6	3.7	3.1	0.6
Hughes V	2.96	1.3	1.3	0.1	6.0	10.0	3.7	5.4	8.3	4.4
Hughes V	3.04	4.1	3.0	4.8	3.4	−4.5	5.3	8.0	0.7	4.7
Grant V	3.03	4.1	3.7	3.3	3.3	−4.3	8.4	7.6	7.3	8.0
Grant V	1.91	4.8	1.3	6.3	6.8	2.4	0.4	10.3	12.0	14.3
Brenda V	2.13	3.8	3.4	3.0	1.0	3.3	5.0	7.7	4.5	5.0
Brenda V	1.90	3.0	3.0	1.6	4.8	0.0	4.4	5.6	6.0	7.8
Arithmetic mean error		4.1	3.6	5.7	5.9	0.0	8.0	8.9	8.8	8.4
Standard deviation		4.9	6.7	5.1	5.1	7.8	5.3	4.0	5.4	5.8
RMS error		6.3	7.6	7.7	7.7	7.8	9.0	9.7	10.3	11.1

Errors shown in brackets are the most conservative possible, and tend to be approximately 3 units of per cent lower than their probable probable values.

greater than 0.1 mv were obtained in 67 per cent of a total of 756 measurements and in over 10 per cent of the cases amplitude differences exceeded 0.3 mv.

Details of percentage errors in QRS amplitudes calculated according to the foregoing formula are shown in Table III. The errors were calculated using the quantities A_+, B T a b and t = 1 (see under *Method*). For a few large errors the most conservative possible estimates of the error using B_- and b_+ are shown in parentheses. The ECG which the direct writers reproduced with the greatest error was Shelley V, the direct writer showing the greatest over all error was #70117. On this instrument, Shelley V, showed an error of at least 63.4 per cent, which is the amount by which the direct writer complex should be increased to obtain the true value. Since this is the most conservative possible estimate, the actual error was probably 68 per cent and may have been as high as 73 per cent. Errors that exceeded 15 per cent were noted in 22.1 per cent of the cases, but errors were generally greater for small QRS amplitudes—a fact largely due to our means of expressing them. How

writers

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Errors for individual ECG complexes: Arithmetic mean	Errors for individual ECG complexes: RMS
8.7%	11.3%	8.3%	11.3%	13.4%	13.5%	15.9(13.3)%	26.9(26.1)%	36.3(24.3)%	—	—
18.1	14.7	4.8	14.8	4.8	14.8(13.4)	7.4	29.1(13.8)	33.6(24.1)	—	—
10.1	13.8	3.3	16.3	2.5	23.4(21.4)	3.8	14.8(14.1)	31.6(20.8)	—	—
8.8	16.4	4.5	11.9	7.4	18.8(17.6)	8.3	23.3(22.2)	26.8(23.1)	—	—
14.3	17.3	14.0(16.9)	20.3(18.7)	22.6(21.0)	30.1(24.2)	26.2(21.0)	41.7(30.7)	46.8(30.4)	5.6	22
4.8	8.7	4.0	8.1	−0.3	11.3	3.9	3.8	17.3(14.8)	—	—
8.7	12.5	5.4	16.7(15.5)	26.3(15.4)	15.5	23.0(21.3)	31.0(23.0)	31.7(23.1)	—	—
3.8	4.8	1	6.3	2.3	11.3	2.9	15.8	19.6(15.3)	—	—
7.8	10.6	2.8	8.8	2.1	6	10.3	14.8	14.8(13.3)	—	—
30.0(31.3)	23.8(21.7)	27.0(24.7)	25.0(27.0)	32.3(33.0)	25.0(28.7)	30.0(24.0)	54.0(40.1)	46.8(41.1)	27.1	29.4
4.6	7.4	−0.7	8.8	8.1	0	13	17.9(15.0)	17.8(16.0)	—	—
3.9	10.3	4.3	7.1	10.7	17.8(16.3)	1.3	30.8(18.0)	21.3(21.8)	—	—
6.2	13.0(11.4)	−4	6.6	1.3	3.3	7.3	5.5	20.3	—	—
6.9	8.3	6	10.1	1.9	18.1(16.0)	3.3	21.4(20.3)	25.9(23.1)	—	—
7.8	13.8	1.8	13.6	10.5	14.8(14.3)	16.2(13.1)	30.3(27.0)	21.8(20.0)	—	—
17.3(13.0)	14.4	22.8(21.3)	22.8(20.4)	22.8(21.0)	30.0(24.0)	30.3(27.0)	41.0(30.2)	27.2(24.7)	20.3	22.8
13.8	10.6	−0.3	15.1(13.0)	12.3	21.7(21.0)	15.7(14.0)	30.4(20.0)	25.5(27.4)	—	—
11.6	8.8	10.1	13	6.8	27.1(23.0)	8.6	23.3(20.0)	23.3(22.7)	—	—
10.3	21.8(18.0)	7.0	1.7	24.2(22.0)	14.9	27.3(21.0)	30.4(27.0)	30.4(27.0)	—	—
7.6	6.4	8.3	6.4	4.9	10.5	13.1(13.0)	19.0(18.0)	27.0(23.0)	—	—
8.8	7.4	−6.9	10.3	2.8	3.4	14.3	14.3	13.8	—	—
1.4	6.6	7	10.5	0.9	10.7(21.0)	10.3(13.0)	30.1(18.0)	23.8(22.0)	—	—
13.8	11.9	17.0(13.0)	16.6(15.0)	14.3	23.4(20.4)	25.4(23.0)	31.7(30.0)	32.0(30.0)	—	—
17.0(13.0)	14.4	13.0(13.0)	20.1(17.0)	13.3(12.0)	27.3(24.7)	25.3(25.0)	33.3(31.0)	30.7(27.0)	4.3	5.9
10.1(14.3)	11.9	6.6	13.7	13.8	14.0	30.4(30.0)	33.7(30.0)	22.7(20.0)	—	—
3.4(18.3)	18.4(16.5)	33.3(28.0)	29.9(27.0)	15.6(15.5)	25.8(27.1)	47.3(34.4)	34.9(23.0)	42.3(28.0)	26	23.5
2.3	8.8	−4.8	4.7	−4.0	3	−4	8.5	10.9	—	—
1	2.3	−15.3	8.8	4.7	5.7	1.3	4.2	1.5	—	—
10.3	1.0	13.3	12.6	11.8	8.1	30.4(27.0)	23.0(20.0)	22.4(20.0)	—	—
30.7(26.3)	30.1(31.0)	27.0(24.0)	34.7(25.0)	44.6(40.5)	42.3(30.0)	42.7(30.0)	43.3(37.5)	67.3(30.0)	27.3	29.6
8.8	12.6	6.3	8.9	[illegible]	[illegible]	33.9(22.3)	22.4(22.0)	18.8(17.0)	—	—
12.1	[illegible]	33.0(20.0)	[illegible]	30.4(24.0)	34.3(27.0)	43.3(40.3)	38.7(33.7)	31.9(20.1)	30.7	34.5
3	13.1	6.7	13	1.6	11.1	21.1(19.7)	30.4(25.1)	14.7(15.0)	—	—
	7	7.1		[illegible]	11.3(13.5)	30.3(33.7)	28.9(24.1)	28.3(24.1)	—	—
5.6	8.8	5	8.1	−6.0	2.0	7.7	16.3	10.3	—	—
1.7	8.8	3.7	0	−10.5	7.6	−4.4	7.4	4.8	—	—
4.5	8	−13.3	8.2	−6.9	1.0	−8.3	7.3	0	—	—
4.0	7.8	−6.5	8.3	−6	4.4	4.8	1.3	3.5	—	—
5.0	10.5	−0.3		2	3.3	8.8	18.3(14.2)	9.9	—	—
0.2	18.8	18.8	13.0	−4.1	18.3(14.0)	14.2	23.4(24.1)	28.3(24.0)	—	—
6.1	1.3	−0.3	0	4.1	4.0	9.3	4.0	1.0	—	—
4.3	7.4	−4.4		3.4	[illegible]	6.6	13.3(13.0)	13.0(14.3)	—	—
7	3.7	8.3	13.5	3.3	13.3	10.3	22	24.3		
6.4	3.8	13.8		13	10.5	4.3	13.5	23.9		
7	13.8	5.0	14.0	14.0	13.7	25.6	26.4	27.8		

values. Other tabulated figures are also conservative and, in general, tend to be approximately [illegible] units of per cent lower than their

ever th amplitude in Allison V is quite large (2.2 mv.) yet three instruments showed errors which on the most conservative basis, exceeded 15 per cent

The occurrence of negative errors represents those cases in which the normalized direct writer response exceeded that of the control. To arrive at a single figure-of-merit for each instrument, which would not allow positive and negative errors to cancel, root-mean-square (RMS) errors were calculated. These are shown in the bottom section of Table III together with the arithmetic means and standard deviations. The instruments have been listed in order of increasing RMS error. RMS and arithmetic mean errors for a few individual ECG complexes producing the largest errors are shown at the right-hand side of the table; these were calculated using the quantities A_+, B, T, a, b and t − T. In 6 out of 42 complexes the direct writers showed RMS errors exceeding 20 per cent.

All of the above mentioned errors arise from two sources: (1) error in the calibration circuit, resulting in an incorrect setting of its sensitivity, and (2) inadequate response to high frequencies. Internal cali-

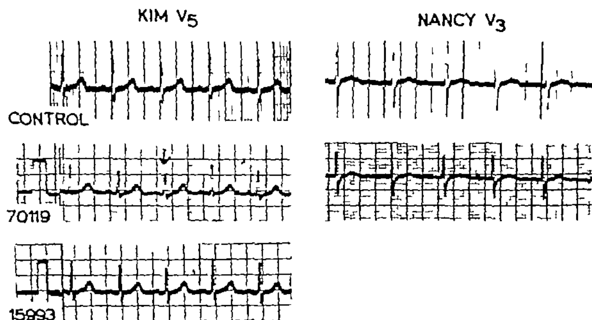


Fig. 4. Kim V_5. Severe clipping of S waves in one direct-writer (*70119*) but much less in another (*15993*) despite similar appearance of their calibration tracings. Nancy V_3. U and P waves and details of T waves are almost suppressed in the 70119 tracing as compared with the control. Note also diminution in QRS amplitude—error at least 4 6 per cent. The tracings were taken at the same sensitivity. (Noise on control tracing, when present was added to line width and deducted in determinations of amplitude.)

frequency responses in excess of minimum standards set up by the American Medical Association. This may imply a cutoff frequency of 31 c.p.s. or of 50 c.p.s. depending upon whether the original or the revised recommendations are referred to. (The A.M.A. discontinued testing electrocardiographs in 1955.) Table IV indicates that 5 of the 18 instruments tested failed to meet the original A.M.A. requirement, and 16 failed to meet the A.M.A. revision. Our results indicate that to minimize instrument errors of direct writers, cutoff frequencies should probably not be less than 100 c.p.s. under normal operating conditions. Furthermore the impossibility of predicting accurately the upper cutoff frequency from the shape of the calibration tracing would indicate a need for a simple device which would permit at least a rough estimate of this frequency.

In many assessments of a desirable frequency response less attention has been paid in the past to the effect that a limitation of the frequency response would have on amplitude than to other features of the wave form. One of the earliest comparisons between different types of electrocardiographs was carried out in 1929 by Ernstene and Levine, who concluded "Since the curves obtained with the amplifier type instrument [which they were evaluating] were essentially the same as those recorded by the string galvanometer except for slight differences in the amplitude, they may be considered satisfactory."[11] Yet scrutiny of their published data shows that if the differences in the heights of the R waves recorded with the string galvanometer and the amplifier type of recorder are expressed as percentages of the height of the corresponding R waves recorded with the amplifier type instrument—a procedure analogous to that described in the present paper in 6 out of 75 instances the error exceeded 30 per cent and the median value was 13 per cent. It should be noted that at the time their study was made, diagnostic significance was not attached to measurements of amplitude. In 1953 Kerwin concluded "In some cases, except for slight loss of amplitude of *QRS*, little or no change could be found when a frequency above 47 cycles per second (three decibels down) was used at normal paper speed and standardization. In others ade-

Cardiac involvement in lymphosarcoma and reticulum cell sarcoma

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Involvement of the heart by malignant neoplasms has been considered to be relatively uncommon. Theories advanced to explain this low incidence include metabolic peculiarities of the heart muscle, restricted lymphatic connections of the heart the strong kneading action of the heart muscle and the rapid flow of blood through this organ Scott and Garvin[1] stated that spread via the coronary arteries was the most frequent mode of metastasizing to the heart and considered involvement by retrograde lymphatic flow to be less frequent than direct extension from the lungs or mediastinal nodes. The most common mode of involvement of the parietal pericardium was by extension of intrathoracic tumor These concepts have been generally accepted In the case of malignant lymphomas one must also consider the possibility of multicentric origin which may involve the heart as one of the initial sites. Both primary and metastatic lesions of the heart have been reported in cases of malignant lymphomas, but secondary involvement is by far the more common.

The first report of cardiac involvement in a case of malignant lymphoma appeared in 1870 when Murchison described a case of Hodgkin's disease involving the heart. Very few additional cases were reported prior to 1939 Since then data have become available from several autopsy series as well as from individual case reports.[2-4] The total number of reported cases has increased sufficiently to permit at least a superficial analysis of this complication. It is apparent that the lymphomas are among the tumors which involve the heart relatively frequently with cardiac lesions found at autopsy in about 20 per cent of the cases. Other neoplasms in which cardiac involvement is relatively common include malignant melanoma bronchogenic carcinoma and carcinoma of the breast.[1,4,6,7]

Table I presents data from several series in the literature on the frequency of cardiac involvement found at autopsy in the three principal histologic types of lymphoma. It is clear that such involvement is most common in reticulum cell sarcoma. The relative frequency of involvement in lymphosarcoma and Hodgkin's disease varies from one series to another Bisel Wroblewski and LaDue found the heart to be involved more frequently in Hodgkin's disease whereas DeLoach and Haynes reported the reverse. The combined experience indicates that cardiac lesions occur about twice as frequently in lymphosarcoma

Most authors agree that the diagnosis

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Table I Frequency of cardiac involvement in the lymphomas found at autopsy in several reported series

Authors	Lymphosarcoma			Reticulum cell sarcoma			Hodgkin disease		
	Autopsies	Cases with cardiac involvement	Per cent	Autopsies	Cases with cardiac involvement	Per cent	Autopsies	Cases with cardiac involvement	Per cent
Scott and Garvin[1]	13	1	8	9	6	67	22	1	5
Herbut and Maisel[3]	16	3	19				13	2	15
Jackson and Parker[4]				28	6	21	98	3	3
Bisel, et al.	15	2	13	23	7	30	31	8	26
DeLoach and Haynes	33	14	42	45	18	40	49	3	6
Nabarro[5]	27*	6	22	9	5	56	24	5	21
Jakob and Zirkin[10]							15	3	20
Totals	104	26	25	114	42	37	252	25	10

*Includes lymphocytic leukemia.

of cardiac involvement is difficult to make during life. Among the findings which have been described as suggestive of involvement of the heart or pericardium are pericardial effusion, intractable heart failure, cardiac arrhythmias or heart block, and low voltage in the electrocardiogram.

This paper presents the results of a study of cardiac involvement in lymphosarcoma and reticulum cell sarcoma made at the Roswell Park Memorial Institute. Particular attention was paid to the correlation of clinical findings with the lesions seen at postmortem examination.

Material

The autopsy protocols of patients who had died of lymphosarcoma and reticulum cell sarcoma at this Institute during the period 1916-1959 were reviewed. All patients who die at the Institute undergo postmortem examination so that this series is not influenced by selection in so far as permission for autopsy is concerned. A total of 211 cases were reviewed: 170 of these were classified as lymphosarcoma and 41 as reticulum cell sarcoma. The clinical records of patients found to have gross or microscopic involvement of the heart or parietal pericardium were reviewed in detail and an attempt was made to correlate clinical manifestations and electrocardiographic findings with the anatomic lesions.

The majority of patients were middle aged or elderly persons, and many had a history of heart disease antedating the diagnosis of lymphoma.

Results

The incidence of cardiac involvement and the distribution of the metastatic lesions are summarized in Table II. Fifteen per cent of the patients with lymphosarcoma and 27 per cent of the patients with reticulum cell sarcoma were found to have lesions of the heart or pericardium. In both diseases the heart was more frequently involved than the pericardium and only 4 patients are known to have had pericardial lesions alone.

Table III summarizes the character of the metastatic lesions. When the pericardium was involved gross lesions were frequently seen. However, the majority of lesions in the heart (including epicardium) were microscopic.

No correlation was found between the duration of the disease and the presence or degree of cardiac involvement. Some

cardiac involvement during life are pericardial friction rub and pericardial effusion. The latter is often difficult to diagnose in patients with enlarged mediastinal nodes large pleural effusions or pulmonary infiltration near the heart When signs suggestive of cardiac tamponade appear however pericardiocentesis is indicated In our experience this procedure has not been attended with undue morbidity and has often resulted in dramatic clinical improvement When evidence of cardiac involvement is obtained appropriate treatment should be instituted promptly We prefer irradiation of the cardiac area as the definitive therapeutic modality

Summary

Cardiac involvement was found at autopsy in 15 per cent of 170 patients who died of lymphosarcoma and in 2? per cent of 41 patients who died of reticulum cell sarcoma The heart and epicardium were involved more frequently than the pericardium which suggests that cardiac lesions arise from hematogenous dissemination rather than by direct extension from mediastinal tumor masses Pericardial effusion appeared to be associated with myocardial and epicardial infiltration rather than with pericardial involvement the presence of bloody pericardial fluid suggested infiltration of the epicardium. Except for pericardial friction rub and clinically demonstrable pericardial effusion there were no clinical or electrocardiographic manifestations which represented reliable signs of cardiac involvement.

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pattern present in the ventricular premature contraction 42 electrocardiograms in 39 patients.

Subsequently the hospital records of all these 144 patients were studied. Special attention was given to the clinical and laboratory evidence of myocardial infarction in the past (sustained precordial pain accompanied by sweating hypotension fever increased level of transaminase in the blood fast sedimentation rate etc.) The presence of arteriosclerosis in areas of the vascular system other than the coronary arteries (cerebral carotid femoral arteries etc.) was determined on a clinical basis.

Results

Group I Ventricular premature contraction with an infarction pattern (qR or QR) and sinus beat with normal pattern. The review of patients records revealed that 16 of these 59 patients (27.2 per cent) had had unquestionable evidence of myocardial infarction in the past by history and laboratory criteria and 43 patients (72.8 per cent) did not have definite evidence of myocardial infarction (Figs. 1 and 2). Twelve of the 43 patients had a history of repeated episodes of angina pectoris. All 28 of these patients (16 with myocardial infarction and 12 with angina pectoris) had abnormal electrocardiograms indicative of significant myocardial ischemia.

Of the other 31 patients 19 had had no history of myocardial infarction or angina pectoris. Sixteen of the latter number had definitely abnormal electrocardiograms with evidence of myocardial ischemia conduction defect ventricular hypertrophy or abnormality of rhythm. In addition *several had evidence of arteriosclerosis in* other areas of the vascular system (cerebral iliac femoral and carotid arteries). Therefore it was reasonable to assume that they had involvement of the coronary arteries which resulted in ischemic heart disease.

Twelve patients of the total 59 (20.1 per cent) in this group remained and all have had no history of angina pectoris myocardial infarction or evidence of arterial occlusive disease and all had normal electrocardiograms.

Four of these 12 patients were less than 50 years of age (26 31 41 and 42 years of age). The 31 year-old patient had undergone a left ventriculotomy during an operation for correction of mitral stenosis. The other 8 patients were all more than 50 years of age (average age 62 years).

Nevertheless these 12 cases were considered to be "false positive" by the ventricular premature contraction criteria for diagnosis of ischemic heart disease and represents an *overdiagnosis rate of 8.3* per cent.

The infarction sites as located by the ventricular premature contraction were as follows (a) 29 anterior and septal *(b) 15 inferior (c) 8 multiples (d) 4 posterior* (e) 3 lateral.

Group II Signs of myocardial infarction present in the sinus beat. The ventricular premature contraction did not show the pattern of myocardial infarction.

In this group there were 24 patients (60 per cent) in whom evidence of myocardial infarction was documented by methods (clinical and laboratory) other than electrocardiography. Sixteen had had no history of myocardial infarction. However 8 of these patients had repeated episodes of angina pectoris. The other 8 were asymptomatic yet all of them had marked ischemic abnormalities in the electrocardiogram. Therefore every patient had either clinical or laboratory evidence of ischemic heart disease.

In none of the above mentioned cases was the ventricular premature contraction suggestive of an infarct and as a result they were considered to be false negative by this criteria *(Figs. 3 and 4). We should* add that these ventricular premature contractions were recorded in the same lead *in which myocardial infarction* was diagnosed in the sinus beat.

Group III Signs of myocardial infarction in the sinus beat and the ventricular premature contraction. The review of patients records revealed *that 24 of the 39* (61.5 per cent) had had a myocardial infarction in the past and 15 patients (38.5 per cent) denied any history of coronary occlusion. Among these 15 patients without myocardial infarction 5 had angina pectoris and 10 had a negative history of either myocardial infarction or angina

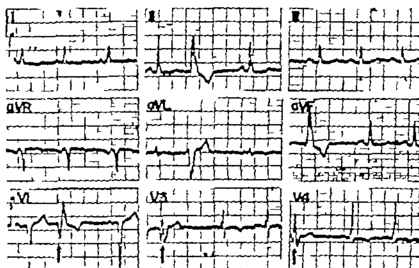


Fig. 1. Group I. Electrocardiogram showing myocardial ischemia in the sinus beat without evidence of myocardial infarction. The ventricular premature contraction recorded in Leads V and V (arrows) show definite Q waves suggestive of anteroseptal myocardial infarction.

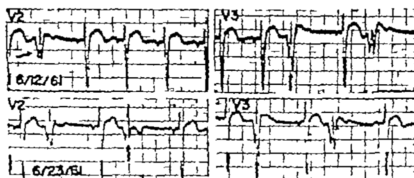


Fig. 2. Group I. Leads V and V taken 11 days apart demonstrate the constancy of the myocardial infarction pattern (qR) in the ventricular premature contractions (arrows) which occur in bigeminal fashion. Note that the sinus beat does not indicate infarction.

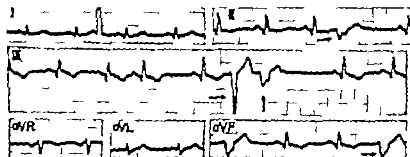


Fig. 3. Group II. The sinus beat shows pattern of inferior myocardial infarction. Several ventricular premature contractions seen in Leads II, III and aV$_F$ (arrows) arising from different foci do not show the qR configuration.

pectoris. Nevertheless, all of these 10 other patients had definitely abnormal electrocardiograms that were indicative of myocardial ischemia. Therefore all patients in this group had significant evidence of ischemic heart disease and the ventricular premature contraction and the sinus beat agreed in the diagnosis of myocardial infarction (Figs. 5 and 6).

Discussion

Ventricular premature contractions usually simulate the pattern of ventricular activation in bundle branch block. When the configuration is that of left bundle branch block, the stimulus has arisen from the contralateral ventricle. Similarly a ventricular premature contraction with right bundle branch block pattern has its origin in the left ventricle. Previously Bisteni and associates[1] demonstrated the production of ventricular premature contractions which approached the contour of normal sinus beats despite existing bundle branch block. When the stimulus arises in the homolateral ventricle and between the onset of the P waves and the beginning of the QRS, the ventricular premature contraction is less bizarre as the P-R interval approaches that found in normal sinus conduction. Variations about this normal time sequence create the respective aberrations in the ventricular premature contraction.

Harris, studying the site of the origin of ventricular premature contractions in the infarcted dog heart, found that ectopic discharge within the first few minutes after coronary occlusion arose in the boundary between the ischemic and normal myocardium. Chronic experiments resulted in a similar conclusion. Furthermore, moderately hypoxic heart muscle has been shown to be hyperexcitable and can give rise to ventricular premature contractions.

Bisteni and associates[2] have demonstrated that ligation of the anterior descending branch of the left coronary artery in dogs was followed by excitation of the infarcted area and produced ventricular premature contractions with an infarct morphology (qR or QR pattern). The results were then extrapolated to clinical material and the diagnosis of myocardial infarction has been made possible with that technique. However, in their series of electrocardiograms from human beings no mention was made of the incidence of possible "*false positive*" diagnoses of myocardial infarction using the ventricular premature contraction criteria. This information is of significant practical value.

According to our present series of cases, the diagnosis and location of myocardial infarction, either acute or old, can be made with a significant degree of accuracy by an analysis of the ventricular premature contraction (Fig. 5).

From our data we found that with the ventricular premature contraction criteria the diagnosis of myocardial infarction was made in 12 tracings from apparently normal subjects out of 144 electrocardiograms, giving an incidence of "false positive" of 8.3 per cent. This figure is within the acceptable limit of overdiagnosis and when correlated with the clinical findings makes the method quite useful for practical purposes. In addition, this method failed to detect the presence of myocardial infarction in 43 tracings, giving an incidence of "false negative" results of 29.8 per cent.

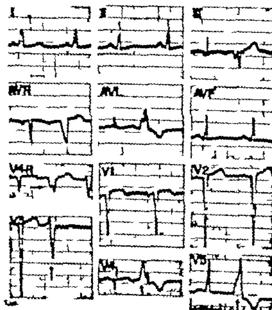


Fig. 4. Group II. Electrocardiogram showing the pattern of anteroseptal myocardial infarction. Ventricular premature contractions recorded in Leads V4R, V, V and V (arrow) do not show the infarction pattern.

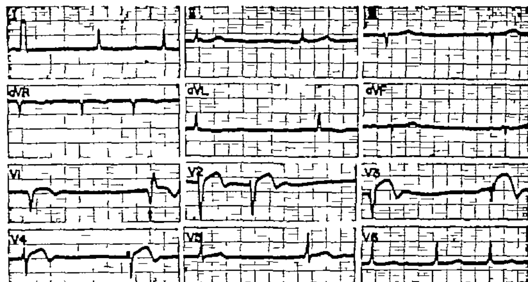


Fig 5 Group III Electrocardiogram showing the pattern of acute anteroseptal myocardial infarction One ventricular premature contraction recorded in Lead V (*arrow*) shows the QR pattern with S-T segment elevation.

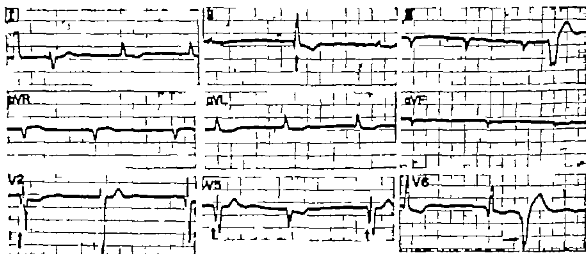


Fig 6 Group III Electrocardiogram showing the pattern of an inferior and anteroseptal myocardial infarction. Ventricular premature contraction in Lead II shows QR pattern as do those in Leads V_2, V_5, and V_6

The pattern of myocardial infarction was present in the sinus beat of the 12 lead electrocardiograms in all of these 43 patients, and there was clinical and laboratory evidence to support the diagnosis of ischemic heart disease

On the other hand the data from Group I (normal or equivocal sinus beat with the ventricular premature contraction displaying the pattern of infarct) demonstrated that the diagnosis of myocardial infarction had been missed or equivocally made in 27 2 per cent if the sinus beat were used as the sole criterion for the diagnosis.

On the basis of these results, it is suggested that this method provides additional useful information for the diagnosis of ischemic heart disease. In several cases, multiple ventricular premature contractions of infarction type not only correlated well with the location of the infarct determined in the sinus beat, but, indeed implied a wider area of necrosis than was evident in the sinus beat.

Summary and conclusions

1. A study of the ventricular premature contraction showing a qR or QR morphology was made in the 144 electrocardiograms which demonstrated this pattern from an original group of 1,193 electrocardiograms which displayed any type of ventricular premature contraction pattern.

2. The analysis of the electrocardiographic configuration of a ventricular premature contraction may offer a clue to the presence of myocardial infarction when the infarction is not demonstrated in the sinus beat, or is masked by a conduction defect.

3. The "infarction" ventricular premature contraction is capable of adding further information to that derived from analysis of the sinus beat by helping to locate the area and extent of necrosis.

We wish to thank Miss Ellen Wright and Mrs. Alzemar Carvalho for their help in the preparation of this report.

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mean arterial blood pressure remain below control levels. Thus, the most persistent toxic effect seems to be that of vasodilatation.

Serum concentrations of quinidine were measured in 4 animals. Immediately after the infusion of quinidine serum concentrations ranged between 15 and 45 mg per liter. In the animal whose serum concentration of quinidine reached 45 mg./L. the drug was infused at a slightly higher concentration than usual (i.e. total 65 mg./kg. of body weight) but at the same rate and for the same period of time as in other studies. The rather prompt rise to a high serum concentration was followed shortly by cardiac arrest and then by respiratory arrest. Artificial respiration and external cardiac massage were ineffective, and the animal died. A sample of myocardium taken about 5 minutes subsequent to the cardiac arrest revealed a concentration of quinidine of 93 μg per gram of muscle wet weight. In 2 animals the serum concentration of quinidine was followed as the animals spontaneously recovered. In the first animal the initial serum concentration of quinidine was 28 mg./L. At the end of ½ hour it had fallen to 8.4 mg./L. at the end of 1½ hours the concentration of quinidine in the serum was 5 mg./L. In the second animal the initial concentration of quinidine in the serum was 24 mg./L. At the end of ½ hour after the infusion was terminated the serum concentration fell to 11 mg./L. At the end of 1 hour it was 8 mg./L., and at the end of 1½ hours it was 10 mg./L. Within 10 minutes after the blood for the last determination of serum quinidine was obtained this animal was sacrificed. The myocardial concentration of quinidine was 457 μg per gram of muscle wet weight.

The blood pH fell very slightly after infusion of quinidine. In 8 animals the fall averaged 0.06 pH units. As the animals spontaneously recovered the blood pH gradually increased although at the end of 2 hours it did not return to the control pH. No significant changes in the serum concentration of sodium were noted during the infusion of these large amounts of quinidine but serum concentration of potassium fell in all cases, the average fall being 0.7 mEq. per liter. After infusion of the drug the myocardial concentration of water was within the normal range for our laboratory. In 2 dogs the myocardial concentration of potassium was determined and the values were 84 and 89 mEq. per kilogram of muscle wet weight respectively. The myocardial concentrations of sodium in these same animals were 37 mEq. per kilogram of myocardium wet weight in each. These values are within the normal range for our laboratory.

Reversal of quinidine toxicity (*Fig. 2*). Infusion of each agent that was given to reverse quinidine toxicity was started within 5 minutes after the termination of the infusion of quinidine. Because of the previous results which indicated a stable quinidine effect that ended in most respects, between 30 and 60 minutes, any further effect observed either beneficial or deleterious, was recorded within ½ hour after termination of the infusion of quinidine.

CALCIUM CHLORIDE (FIG. 2,CA). Two grams of calcium chloride in a concentration of 20 mg. per milliliter were infused over a period of 15 minutes in 2 animals. Since the results of the 2 experiments were somewhat divergent, the hemodynamic data will be discussed individually. In one dog the serum concentration of calcium was raised from a control of 7 mg. per 100 ml. to 25 mg. per 100 ml. In this animal there was no increase in the cardiac rate. There was a modest increase in the cardiac output, although it remained below the control. The stroke volume increased 28 per cent above the control. Myocardial contractility was increased. The mean arterial blood pressure decreased and the peripheral vascular resistance was decreased. In the other dog the heart rate was increased 41 per cent above the control and the cardiac output returned to the control level. Myocardial contractility was increased. However the blood pressure was further decreased and the stroke volume was not returned to the control. The peripheral vascular resistance was also decreased. The electrocardiographic changes were similar in both animals. There was no significant shortening of the P-R interval. The QRS duration was actually increased somewhat more by the calcium; it was 0.07 second for the

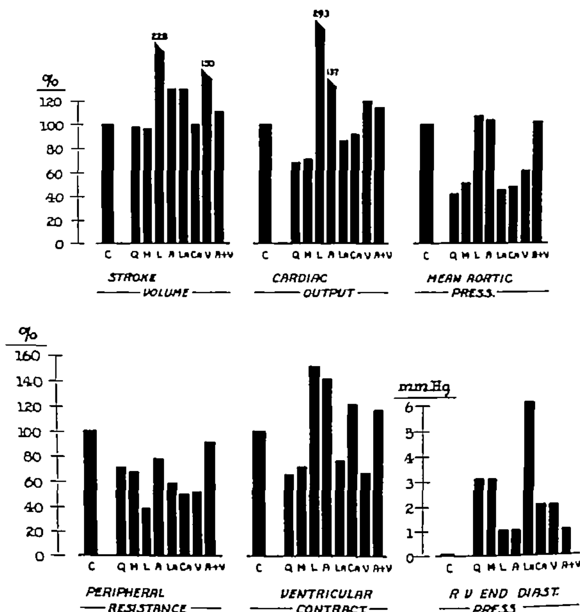


Fig. 2. Treatment of quinidine toxicity. *C*, Control. *Q*, Quinidine. *M*, Methoxamine. *L*, Levarterenol. *A*, Angiotensin. *La*, Molar sodium lactate. *Ca*, Calcium. *V*, Disodium calcium versenate. *A + V*, Angiotensin and disodium calcium versenate. Per cent changes from the control state, arbitrarily designated as 100 per cent, are reflected in the height of the bars. Under calcium, the two sets of data discussed in the text are averaged.

control, 0.09 second after quinidine, and 0.11 second after calcium.

MOLAR SODIUM LACTATE (FIG. 2,La). Two hundred milliequivalents of molar sodium lactate were infused into each of 5 animals over a period of 15 to 20 minutes. The cardiac output was increased almost entirely because of an increase in stroke volume. The mean arterial blood pressure was not significantly changed, and the peripheral vascular resistance was further decreased. The right ventricular end diastolic pressure was increased in all but one dog. Ventricular contractility was increased above control levels in only one dog. When the ventricular contractility after molar sodium lactate is compared with the ventricular contractility after quinidine in the same animals, the results are found to be variable. In 2 dogs the ven

of large amounts of quinidine into anesthetized dogs, it would appear that variations in the dosage and rate of administration of quinidine and the nature of cellular uptake can account for at least two forms of quinidine toxicity. When a large amount of the drug is given rapidly intravenously, the free concentration of quinidine in the interstitial fluid rises abruptly with the result that a large amount of drug is bound to membrane phospholipid and/or protein. As a result of altered ionic movements and electrical activity at the membrane, ventricular tachycardia, ventricular fibrillation, or cardiac arrest can occur. Under these circumstances, cardiac arrest occurs as a consequence of blockage of the membrane potential at the resting level. On the other hand, if quinidine is given more slowly or in smaller doses, then the concentration of free quinidine in the interstitial fluid is lower and less drug binds to the cell membrane, which reduces the possibility that the animal will develop a serious arrhythmia acutely. Since quinidine can pass through the cell membrane,[29] more quinidine is bound to intracellular protein as time passes. Hence, a large concentration of intracellular quinidine may be achieved without causing the animal to die, although marked hemodynamic changes due to reduced myocardial contractility and peripheral vasodilatation occur.

The hypotension produced by quinidine is due both to a decrease in cardiac output and to a decrease in peripheral resistance, with the latter predominating. The peripheral vasodilatation is a well recognized effect of quinidine[1] that probably appears in an exaggerated form in the anesthetized animal because of the partial anesthetic inhibition of the otherwise compensating neurohumoral mechanisms. The peripheral vasodilatation has been reported to be due to depression of sympathetic receptors, to direct depression of vascular smooth muscle,[18] and in part to depression of sympathetic ganglia.[12] An antagonism of the cinchona alkaloids to stimulation of the sympathetic nerves or injection of epinephrine and the reverse has been reported by a number of workers.

Further evidence that quinidine competes in some way with the action of sympathomimetic amines on the peripheral vessels derives from the studies of the vascular effects of 4-hydroxymethyl-6-methoxyquinoline, the substituted quinoline ring of quinidine.[4] To reverse the hypotension induced by this agent, 10 to 20 times more levarterenol or angiotensin is required than is needed to combat other forms of hypotension. Whatever the fundamental nature of the competition may be, its existence is an important consideration in the treatment of quinidine toxicity, as noted below.

The effect of these large doses of quinidine on serum and myocardial concentrations of electrolytes and water is of interest. Conn and Wood[13] found in the isolated perfused dog heart that quinidine caused a small accumulation of intracellular potassium as the result of an increased influx of potassium, probably during the resting potential phase of cardiac activity. In this study, myocardial concentrations of potassium and water after infusion of quinidine were within the normal limits for our laboratory. Thus, these results differ from those derived from experiments in isolated hearts, although the previously described small increments in the myocardial concentration of potassium could have been missed through lack of adequate individual control data. Alternatively, our failure to demonstrate an increased myocardial concentration of potassium may have resulted from a compensating loss of cell potassium consequent to respiratory acidosis. Although the decreased blood pH found in our experiments may in part represent hydrolysis of an acid liberating substance, the most important pH effect is probably due to respiratory acidosis. In the dog in which the blood pH was 7.16, respiration was notably inadequate and arterial blood was quite blue. Respiratory depression and even arrest has been reported in other studies in which large doses of quinidine have been administered. In the intact animal, then, the myocardial concentration of potassium after the administration of quinidine may reflect the sum of a direct action of quinidine tending to increase the value and the secondary changes of acidosis tending to reduce it.

All our animals, save one survived the initial infusion of quinidine. The hemodynamic derangements improved slightly in the following hour and at the end of 1½ hours were almost entirely dissipated Consequently any less than dramatic improvement that occurred as the result of drug therapy initiated more than 30 to 60 minutes after quinidine has been stopped must be viewed with some skepticism The effects of all our agents were thus evaluated during this early interval At the same time the necessity of instituting effective treatment at the earliest moment must be emphasized Our animals possessed essentially healthy circulations and were able to withstand shock and poor myocardial contractility More dire results may follow in a subject with an impaired circulation or myocardium. Another point to be made is that the rapid administration of small doses of quinidine may produce an alarming drop in blood pressure at a time when tissue concentrations of quinidine are not high and when the serum levels are only temporarily elevated This hypotension is rather quickly reversed by stopping the administration of quinidine. Any drug that does not harm the circulation might seem to have beneficial effects on this variety of quinidine toxicity But when serum and tissue concentrations of quinidine remain high as in our study comparable to the situation in patients given large doses of quinidine through slow intravenous infusion or repeated oral dosage reversal of quinidine toxicity becomes much more difficult.

Effect of drug therapy on quinidine toxicity Calcium was given on the basis of in vitro experiments which had shown an inhibition of quinidine protein binding by calcium ion. Although rather large amounts of calcium chloride produced an inotropic effect there was no consistent increase in blood pressure or peripheral vascular resistance and the electrocardiographic changes were not reversed

Molar sodium lactate, although given in amounts sufficient to increase blood pH seemed to improve only stroke volume significantly affected the hypotension minimally and did not appreciably improve the electrocardiographic abnormalities. Lee[1] has also studied molar lactate treatment of quinidine toxicity in dogs. The amount of quinidine given however was only half that used in our study He found an increase in blood pressure and heart rate and some decrease in duration of the P R interval and QRS complex. Blood pressure was not returned to control levels. In dogs which were given doses of quinidine more comparable to those used in this study molar sodium latate had no such beneficial effect and in either case when given prophylactically it failed to influence the duration or severity of quinidine intoxication Also, as in our experience, there was no demonstrable lowering of the serum level of quinidine by sodium lactate as originally reported by Bellet[11] Cox and West[9] found that the quinidine-induced changes in the monophasic action potential of the rabbit atria were partially reversed by several sodium salts, including lactate, but that lactate itself was of no value. The conclusion was that the beneficial effect on the monophasic action potential was a consequence of an increased external concentration of sodium. In intact animals however Lee[1] found no significant change in the serum concentration of sodium after the administration of lactate.

Methoxamine was ineffective even in large doses with respect to raising the peripheral resistance or systemic blood pressure. Even levarterenol a potent vasoconstrictor failed to increase peripheral vascular resistance and in 4 of 5 dogs there was actually a slight decrease in the calculated value. This finding serves to emphasize the point that quinidine can be a potent vasodilator so much so that it virtually paralyzes the responsiveness of the peripheral vessels to potent vasoconstrictors.

In the treatment of quinidine toxicity the means by which the blood pressure is restored would seem to make a considerable difference. In the anesthetized dog given large amounts of quinidine levarterenol increased the blood pressure only by increasing cardiac output Translated to a patient with intrinsic myocardial disease this result might be undesirable. Angiotensin on the other hand particularly in combination with disodium calcium versenate markedly increases peripheral vascular resistance and enhances the myocardial contractility depressed by quini-

dine. A more physiologic restoration of the circulatory indices is achieved with this therapy. The use of disodium calcium versenate was purely empirical and we have as yet no explanation for its synergistic effect with angiotensin.

None of the therapeutic agents employed in our study produced a decrease in the serum or tissue concentration of quinidine. Once drug administration was stopped spontaneous recovery from quinidine toxicity proceeded unaltered. Until a compound is available that will selectively displace quinidine from sites of critical activity or one that will speed its inactivation, the therapy of choice for quinidine toxicity would seem to be the intravenous infusion of angiotensin or preferably angiotensin and disodium calcium versenate given in combination for a period of 30 to 90 minutes or until the major circulatory effects of quinidine have been dissipated.

Summary

Quinidine toxicity was studied in the intact anesthetized dog. Large doses of quinidine resulted in a decrease in the heart rate, cardiac output, mean aortic blood pressure, ventricular contractility, and calculated total systemic peripheral vascular resistance. The right ventricular end diastolic pressure increased in all dogs. The P-R interval and QRS duration were also increased. Reduction in the calculated total systemic peripheral vascular resistance was the most persistent toxic effect.

Calcium, molar sodium lactate, disodium calcium versenate, methoxamine, levarterenol, and angiotensin were used in an attempt to reverse the hemodynamic alterations induced by quinidine. Of these agents angiotensin was the most effective in reversing the signs of quinidine toxicity. The infusion of angiotensin in combination with disodium calcium versenate proved to be even more effective than the infusion of angiotensin alone. This combination is recommended for the treatment of severe quinidine intoxication.

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intracellular calcium may represent a pool or reservoir of calcium which under certain conditions can be made available to the heart.

If the influx of calcium ions links excitation with contraction then the close morphologic association between the membranes through which these ions must permeate and the intracellular contractile components whose activity they modify becomes increasingly significant,[illegible] as does the magnitude of the surface area over which ionic exchange can occur. Although strontium ions can establish the link between excitation and contraction in a manner comparable with that displayed by calcium[illegible] they do not duplicate the role played by calcium ions in maintaining the resting potential[illegible] and therefore in regulating the selective permeability of the membrane.

The dependence of the strength of contraction on the concentration of extracellular calcium is already well documented for cardiac muscle,[illegible] and recent studies indicate that this dependence is a direct function of the quantitative relationship which exists between the magnitude of calcium influx that occurs during the depolarized state and the concentration of extracellular calcium.[illegible] Weidmann,[illegible] using a turtle heart perfused at low temperatures demonstrated that a change in the concentration of extracellular calcium effected during depolarization influenced the amplitude of the resultant contraction. His results, together with those of Niedergerke,[illegible] indicate that calcium ions influence cardiac contractility even when injected after the onset of the excitation-contraction cycle, i.e. during depolarization. The influx of calcium ions during depolarization is seemingly independent of the means whereby depolarization is evoked whether by electrical stimulation or after a raised concentration of extracellular potassium.[illegible]

Several well-established phenomena associated with the normal functioning of cardiac muscle can be interpreted in terms of this calcium influx which occurs during depolarization and whose magnitude is determined in part by the concentration of extracellular calcium. The relationship between twitch tension and end-diastolic fiber length expressed in the classic Frank-Starling law of the heart[illegible] may simply be the expression of the enhanced calcium influx associated with depolarization in stretched ventricular muscle.[illegible] Similarly the staircase phenomenon[illegible] and post-stimulation potentiation[illegible] probably result from the enhanced concentration of intracellular calcium resultant upon the increased frequency with which depolarization and hence with which the influx of calcium ions occurs within a given time interval.[illegible] Analysis of tension duration curves[illegible] and of other data[illegible] similarly point to a calcium basis for these phenomena.

The relationship between contractility and rhythm expressed in the staircase phenomenon has been noted during experiments in intact animals[illegible] when applied to conditions found in failing hearts it follows that extrasystolic contractions play a significant role in maintaining contractility in these hearts, since by increasing the over-all frequency with which depolarization occurs these extrasystolic contractions will enhance the twitch tension produced at any given end-diastolic fiber length.

In propelling blood through the vascular system the heart functions as a pump and in so doing expends energy. In accordance with the above mentioned data the work performed by the heart (heart rate × tension) must be determined by the magnitude of the calcium influx associated with each depolarization and by the frequency with which depolarization occurs. Accordingly it is not surprising to find that the "efficiency" with which the heart functions as a pump is influenced by the concentration of calcium ions in the extracellular environment.[illegible] It should be pointed out that such estimates of "efficiency" are based primarily on the assumption that all the energy expended by the heart is transformed into useful mechanical work, an assumption which is unjustified in view of the events including excitation and excitation-contraction coupling which are known to precede the performance of mechanical work, and which must represent energy-consuming steps. Drugs such as ouabain, digitoxin, lanatoside C, 9α fluorohydrocortisone[illegible] which increase the ef

ficiency with which the heart performs mechanical work probably do so via this calcium-regulated pathway.[8] Other drugs including quinidine[44] and certain anesthetics,[45] lower the hearts efficiency and accordingly may act on the same system but in the reverse manner. The action of ions other than calcium (e.g. sodium and potassium) on cardiac contractility and excitability can be explained in terms of the known competition between calcium sodium and potassium for membrane and carrier sites.[46]

If as is indicated above calcium ions be essentially involved in those mechanisms which are responsible for the regulation of the semipermeability of cardiac cell membranes, and if the tension produced during contraction be regulated by the magnitude of calcium influx which occurs during the preliminary depolarization then it necessarily follows that calcium ions play an important part in the maintenance and in the regulation of cardiac excitability and contractility. Cardiac failure whether it be represented by arrhythmias, including fibrillation hypodynamicity or the loss of excitability may be attributable to an impairment of calcium-dependent systems. Similarly those hypertensive states which are characterized by an augmented ventricular output may result from an augmented calcium influx associated with each depolarization. The clinical use of drugs which disturb these calcium-dependent systems[7,8] in cardiac muscle should be preceded by the detailed elucidation of the mechanisms by means of which calcium ions regulate cardiac function. Finally the close morphologic association between the membranes from which these ions are displaced[46] or through which they penetrate and the contractile proteins, the activity of which they modify provides a structural basis by means of which such ionic regulation of cardiac performance can be executed. Further studies will indicate whether or not this association is disrupted in those pathologic conditions which involve histologic changes within the myocardium and which result in impaired cardiac performance.

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Fundamentals of clinical cardiology

Systolic murmurs

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Auscultation of the heart is commonly employed to screen a large population for the presence of heart disease. Auscultation may yield information from which a precise anatomic diagnosis may be made. Less frequently, the functional state of the heart may be revealed and a decision reached about the necessity for further diagnostic studies and perhaps cardiac surgery. One of the most common and most important signs that can be found is the systolic murmur. A systolic murmur may denote organic heart disease, and analysis of the murmur may disclose the anatomy and severity of the lesion. A systolic murmur may be heard when the heart is healthy and the subject is normal in all respects that can be determined; such are the truly innocent systolic murmurs. A systolic murmur may be present when the heart is normal but there is an abnormality of the great vessels or their branches. Finally, a systolic murmur may be present when cardiac function is altered by extracardiac factors such as exercise, excitement, fever, anemia, thyrotoxicosis, pregnancy, beriberi, and widespread Paget's disease of bone. Murmurs associated with these and similar conditions are termed *functional systolic murmurs*. Innocent and functional systolic murmurs must be distinguished from organic systolic murmurs which denote a structural abnormality of the heart or great vessels.

A logical account of systolic murmurs should follow upon a description of the mechanism of their production. The true mode of production of systolic murmurs remains unknown. Knowledge of the behavior of systolic murmurs is based upon the correlation between auscultation and phonocardiography and hemodynamic studies and data obtained at autopsy or at cardiotomy. The most widely accepted theory of the cause of systolic murmurs is that turbulent flow in the circulation is audible, whereas laminar flow is silent.[1,2] This theory appeals because it is easily understood and because lesions known to cause systolic murmurs may be expected to result in turbulence. One is accustomed to the roar of a turbulent river near a waterfall and to the silence of a slowly flowing stream.

In 1883, Reynolds[4] described the factors which govern whether steady flow of liquid through a long, straight, rigid tube is streamlined or turbulent. He proposed a dimensionless index, subsequently called *Reynolds number*. When the Reynolds number is below 2,000, flow is laminar (streamlined); when this value is exceeded, flow is turbulent (random). Reynolds number is calculated from the formula

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$$\text{Reynolds Number} = \frac{(\text{diameter})\ (\text{velocity})}{\text{kinematic viscosity}}$$

(Kinematic viscosity is viscosity divided by density.)

This formula predicts a greater likelihood of turbulence when either velocity or diameter increase, yet murmurs are predicted when blood flows through narrowed vessels or orifices.[3] The difficulty is obviated by considering volume flow rather than velocity. Reynolds number is then calculated from the formula

$$\text{Reynolds Number} = \frac{\text{Flow}}{(2\ \pi)\ (\text{diameter})\ (\text{kinematic viscosity})}$$

Turbulence and murmurs are then predicted with increasing flow and decreasing diameter.

Superficially clinical data support turbulence as the cause of systolic murmurs. Systolic murmurs occur in semilunar valve stenosis, in which there is increased velocity through a narrowed orifice, and in anemia in which kinematic viscosity is decreased and flow may be increased. Increased flow through normal orifices, such as may occur with exercise, excitement, and thyrotoxicosis, may be associated with a systolic murmur. The murmur of severe aortic incompetence is to and fro, and the systolic component is thought to be caused by the increased stroke volume ejected or dilatation of the aorta producing relative aortic stenosis. The systolic murmur of atrial septal defect is caused by increased flow through a normal pulmonary valve. In all these conditions, turbulence is likely and a systolic murmur is audible. However, this does not prove that the murmurs are necessarily caused by turbulence. In fact, there is considerable experimental evidence that turbulent flow in a long rigid pipe is inaudible outside the pipe. Furthermore, conditions in the circulation hardly resemble those of the Reynolds experiments. Flow is pulsatile, the vessels are elastic, the endocardium is irregular, and blood is not a Newtonian liquid.

When liquid flows through a narrow orifice, its velocity rises and its pressure falls (the Bernoulli effect).[9] When the pressure falls sufficiently to approach the vapor pressure of the liquid or of gases dissolved in it, bubbles are formed. This effect, described by Reynolds, in 1883, is called *cavitation*. There is no proof that cavitation occurs in the circulation, but it has been suggested that the bursting of bubbles formed by cavitation when blood is forced through stenotic areas causes noise, the systolic murmur. Wiskind has calculated that the frequency of sound produced by cavitation from gas-entrained bubbles would be far too high to be audible, and concluded that if cavitation plays any part in the production of murmurs it is through vapor bubbles. McKusick[1] and others have concluded that it is most unlikely that cavitation occurs in the circulation. McDonald[12,13] has suggested that eddies or vortices generated at valves or fistulas may be more important than turbulence in causing murmurs. Bruns has calculated that turbulence, even under the rare conditions when it is audible, does not generate sufficient energy to set solid tissues into vibration. Bruns and Rushmer[3,15] consider that vibration of blood is inaudible at the surface of the chest unless the heart, vessels, and chest wall are also vibrating.

Bruns[14] has proposed that murmurs are produced by projections of obstacles, such as valves, endocardial ridges, and endothelial irregularities, into the blood stream. The protuberances are claimed to initiate vortices which cause the blood stream in their wake to oscillate at nearly periodic frequencies with sufficient energy to vibrate the surrounding solid tissues. By an extension of his theory and its mathematical treatment, Bruns[1] accounts for the transmission of murmurs, the characteristic pitch of certain murmurs, and the alteration in the characters of murmurs when they are transmitted to secondary areas. Most murmurs are not pure tones, but are composed of mixed unrelated frequencies. All the theories of the mechanism of murmurs that have been mentioned predict that murmurs accompany increased velocity.

Clinical analysis of murmurs

Systolic murmurs

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Auscultation of the heart is commonly employed to screen a large population for the presence of heart disease. Auscultation may yield information from which a precise anatomic diagnosis may be made. Less frequently the functional state of the heart may be revealed and a decision reached about the necessity for further diagnostic studies and perhaps cardiac surgery. One of the most common and most important signs that can be found is the systolic murmur. A systolic murmur may denote organic heart disease and analysis of the murmur may disclose the anatomy and severity of the lesion. A systolic murmur may be heard when the heart is healthy and the subject is normal in all respects that can be determined; such are the truly innocent systolic murmurs. A systolic murmur may be present when the heart is normal but there is an abnormality of the great vessels or their branches. Finally, a systolic murmur may be present when cardiac function is altered by extracardiac factors, such as exercise, excitement, fever, anemia, thyrotoxicosis, pregnancy, beriberi, and widespread Paget's disease of bone. Murmurs associated with these and similar conditions are termed *functional systolic murmurs*. Innocent and functional systolic murmurs must be distinguished from organic systolic murmurs which denote a structural abnormality of the heart or great vessels.

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or subclavian artery and that is attenuated or abolished by compression of the subclavian artery is not uncommon in children and young adults without evidence of heart disease.[23] A similar murmur may be present with atherosclerosis of these vessels in older individuals.[23,24]

Transmission

The mode of transmission of murmurs is not understood. The systolic murmur and thrill of aortic stenosis are frequently transmitted to the carotid artery and it is probable that such transmission is through the blood stream to the vessel wall.

On the other hand a loud aortic murmur may be transmitted to the wrist. This probably is an example of bone conduction since it is not modified by occluding the brachial artery with a sphygmomanometer cuff. The murmur of pulmonary stenosis is frequently transmitted to the neck[23] and this finding alone should not influence the examiner to change the diagnosis from pulmonary stenosis to aortic stenosis. The murmur of idiopathic muscular hypertrophy of the left ventricle may be confused with that of aortic stenosis,[23-34] but radiation to the neck is unusual.[23-34] Transmission of the apical systolic murmur of mitral incompetence to the axilla and back remains a useful and reliable clinical sign,[23] although the murmur of tricuspid incompetence may radiate laterally when it is maximal at the apex.[23] The murmur of mitral incompetence when it is very loud may also be transmitted upward to the base and neck.[23] This feature complicates the already difficult differential diagnosis between aortic stenosis and mitral incompetence, and the existence of both lesions.

The significance of a systolic murmur that is audible over the back of the thorax depends upon the intensity of the murmur and the size of the chest. Any loud precordial systolic murmur may be heard posteriorly so that this finding is not helpful in differential diagnosis. A murmur confined to or loudest at the back suggests the possibility of an organic extracardiac lesion such as coarctation of the aorta or pulmonary arteries or of pulmonary arteriovenous fistula. In adults with thin chests and in children even softer murmurs are often audible posteriorly but this finding in most adults should alert the examiner to the possibility of a vascular lesion.

Intensity

The factors which govern the intensity of a murmur are complex but include body build, the condition of the lungs, the rate of blood flow, and the severity of the causative lesion. Levine's system of grading[4] from Grade 1, the softest audible murmur, to Grade 6, audible with a stethoscope at a distance from the chest, is most commonly employed. In rare instances a murmur is audible with the unaided ear of the patient and his intimates. Thrills are of little diagnostic importance[23] since they are palpable evidence of a phenomenon better analyzed by auscultation. They accompany loud murmurs, especially when these are low pitched, and usually signify that the murmur is organic.

Loud murmurs are most often organic. The intensity of a murmur does not necessarily increase with the severity of the lesion. In mild semilunar valve stenosis, deformity is minimal, flow is normal, and the murmur is inconspicuous. With moderate stenosis, normal output may be maintained and there is a loud systolic murmur and thrill. When the stenosis is severe, cardiac output and the intensity of the murmur may decrease. In patients with cardiac failure and pulmonary edema the murmur of aortic stenosis may be absent until cardiac output has been increased by therapy. In contrast, when the apical systolic murmur of mitral incompetence is loud, the lesion is usually severe.

Quality and pitch

The characteristics of quality and pitch are determined by the frequency. Murmurs of regular tonal frequency are musical. The quality of a murmur is helpful in diagnosis. This is perhaps less evident for systolic murmurs than when the murmur of aortic incompetence is contrasted with that of mitral stenosis. The systolic murmur of mitral incompetence is frequently high pitched and blowing, whereas the murmur of aortic stenosis is lower pitched and rasping. The systolic murmur of Ebstein's anomaly may be scratchy and superficial.

The innocent systolic murmur that is

heard at the lower left sternal border in children is frequently low pitched and rather musical.[14, 15] The murmur of degenerative aortic valve disease in the elderly is often high pitched and its peculiar quality has led to the term *sea gull murmur*. Musical or sea-gull systolic murmurs may be heard after rupture of a chorda tendinea and have been ascribed to periodic oscillation of the chorda and related structures.

Timing

In 1955 Leatham[44] proposed a classification of systolic murmurs into the ejection type and the pansystolic type. This publication marked a turning point in the art of auscultation and related the nature of systolic murmurs to their pathophysiologic causes. It formed the basis of several subsequent descriptions by Leatham, Wood, and others of the precise auscultatory features of several conditions, notably aortic and pulmonary stenosis,[u, u] atrial and ventricular septal defect,[u] the tetralogy of Fallot, mitral incompetence,[u] and the various forms of pulmonary hypertension.[u] Fowler[u] has classified systolic murmurs into pansystolic and nonpansystolic. The latter include ejection murmurs and short early, mid, and late systolic murmurs.

Ejection murmurs. Ejection murmurs are associated with altered flow through the semilunar valves. Their clinical features are based upon asynchronous contraction of the two ventricles and limitation of the murmur to the ejection period of systole. Aortic ejection murmurs usually commence shortly after the first heart sound and, more important, end a little before the aortic closure sound.[u] The murmur increases in intensity in early to mid systole and decreases again before ending. The interval between the first heart sound and the onset of the murmur corresponds with isovolumetric contraction. The interval between the end of the murmur and the sound of aortic valve closure corresponds to the period between cessation of flow and aortic valve closure. The crescendo-diminuendo nature of the murmur parallels slow, maximal, and reduced ejection. Aortic systolic ejection murmurs are frequently initiated by an aortic systolic click,[u] a sharp sound that occurs shortly after the first heart sound. The sequence that can be appreciated by auscultation is then first heart sound, ejection click and murmur, a short silence, and finally the aortic closure sound followed by the pulmonary closure sound. The most important cause of aortic systolic ejection murmurs is aortic stenosis. An ejection click precedes the murmur in mild stenosis of the aortic valve but is attenuated in moderate stenosis and absent in severe stenosis.[u] An ejection click is unusual in congenital subaortic stenosis and is absent in idiopathic ventricular hypertrophy.[u]

The clear-cut features of aortic systolic ejection murmurs tend to be obscured when stenosis is severe.[u] The systolic click is usually absent, and prolongation of left ventricular ejection together with deformity of the valve modify the sound of aortic valve closure. This sound may be inaudible or may be delayed sufficiently to follow the sound of pulmonary valve closure.[7] If no closure sound is audible in the aortic area, the murmur is recognized by its characteristic location and quality with early to mid systolic accentuation.[44] Reversed splitting of the second heart sound is best appreciated at or below the pulmonary area, where the second heart sound splits in expiration but not in inspiration.[47]

Aortic ejection systolic murmurs are also found with deformity of the aortic valve short of stenosis,[u] in aortic incompetence,[u] dilation or aneurysm of the ascending aorta, and in conditions of increased flow through the valve, notably anemia, fever, and thyrotoxicosis.[u] Aortic ejection systolic murmurs associated with conditions other than aortic stenosis tend to be shorter and less intense and harsh than those caused by aortic stenosis.[44]

Pulmonary ejection systolic murmurs. These murmurs are associated with pulmonary stenosis and increased flow through the pulmonary valve. It must be appreciated that the term *pulmonary ejection murmurs* applies to right and not to left ventricular systolic ejection.

Pulmonary ejection systolic murmurs end before the sound of pulmonary valve closure but usually last at least up to and frequently beyond the sound of aortic valve closure.[u, u] The murmur often drowns the sound of aortic valve closure,[u, u] so that

only a single closure sound is audible in the pulmonary area. Pulmonary valve or infundibular stenosis causes a pulmonary ejection systolic murmur and frequently a thrill. If stenosis of the valve is mild there is usually a systolic click[41, 42, 43]; this is less common in moderate stenosis and is usually absent when the stenosis is severe.[42] With increasing severity of stenosis the sound of pulmonary valve closure becomes increasingly faint and delayed from the aortic closure sound and finally becomes inaudible.[42] Increasing severity of stenosis is related to increased length and late accentuation of the pulmonary ejection systolic murmur.[44] Auscultatory diagnosis of severe pulmonary stenosis is based upon a long loud systolic murmur with late accentuation and an absent or greatly diminished and delayed pulmonary closure sound. The aortic closure sound is lost in the murmur. The pulmonary ejection systolic murmur of Fallot's tetralogy has been studied by Vogelpoel and Schrire.[45] They found that increasingly severe stenosis was associated with a shorter, earlier and quieter murmur. This relationship is the opposite of that found in pulmonary stenosis with intact ventricular septum.[44] In the most extreme example of Fallot's tetralogy, pulmonary atresia, there is frequently no systolic murmur.[45]

Pulmonary ejection systolic murmurs also occur in the absence of organic pulmonary stenosis. The pulmonary ejection systolic murmur caused by increased flow through the valve because of a left-to-right shunt is shorter and more superficial than that caused by organic stenosis.[30, 2] In atrial septal defect the relatively short ejection systolic murmur is followed after a short interval by the sounds of aortic valve closure and delayed pulmonary valve closure. These distinctive features make recognition of this defect by auscultation reasonably simple. Pulmonary ejection systolic murmurs are frequent in anemia, fever, thyrotoxicosis, and after exercise, especially in children. A pulmonary ejection systolic murmur is the most common innocent systolic murmur[13] and may be heard in healthy children with healthy hearts. Increased blood flow may generate ejection systolic murmurs at both semilunar valves. Pulmonary ejection murmurs are a little later and longer than aortic ones, and their crescendo is later.[34] Pulmonary ejection systolic murmurs accompany idiopathic dilation of the pulmonary artery and pulmonary hypertension with dilation of the pulmonary artery.[14] In both these circumstances the murmur is frequently preceded by a systolic ejection click.[14, 42]

Pansystolic murmurs. Pansystolic murmurs are not limited to the period of systolic ejection but are audible throughout systole.[41] This characteristic has led to the synonym *holosystolic murmur*. The association between pansystolic murmurs and regurgitant lesions is responsible for the synonym *regurgitant murmur*. The duration of pansystolic murmurs is related to systole of the left or the right ventricle. The most common cause of pansystolic murmurs is incompetence of the atrioventricular valve. The murmur of tricuspid incompetence begins with the first heart sound and, spilling over the aortic closure sound, terminates with the sound of pulmonary valve closure.[31, 41] The murmur of mitral incompetence begins with the first heart sound and ends at or slightly beyond the aortic closure sound.[31, 38, 41, 43] Pansystolic murmurs are of rather even intensity[38] and lack the crescendo-diminuendo quality of ejection systolic murmurs.[41] The murmur of uncomplicated ventricular septal defect is pansystolic.[41] Incompetence of the atrioventricular valve and ventricular septal defect are lesions which permit regurgitation of blood from a high pressure chamber to a low pressure chamber. Regurgitant flow and the resulting murmur persist for at least as long as a pressure gradient exists between the two chambers, that is, throughout systole.

Regurgitant murmurs may be modified by alterations in the responsible pathophysiology. Leatham[41] and Vogelpoel[34] have described in minute ventricular septal defect a very short early systolic murmur which they believe is due to closure of the defect in the latter part of systole.

When pulmonary hypertension complicates ventricular septal defect, the left-to-right shunt diminishes and the pansystolic murmur becomes less prominent.[41] In severe pulmonary hypertension this mur-

mur disappears and is replaced by a pulmonary ejection systolic murmur[44] the result of dilation of the pulmonary artery. The systolic murmur of the Eisenmenger situation is a pulmonary ejection systolic murmur and does not disclose the site of the communication between systemic and pulmonary circulations.[44]

Effect of respiration

As a result of increased venous return,[44] inspiration tends to increase the intensity and length of murmurs which originate from the right side of the heart.[4,31,41] The pansystolic murmur of tricuspid incompetence is frequently accentuated by inspiration.[31] The murmur of mitral incompetence tends to be louder in expiration.[23] Aortic systolic murmurs and thrills are considerably louder in expiration.[44] Pulmonary systolic murmurs, if anything, are louder in inspiration. The intensity of innocent systolic murmurs is often greatly modified by respiration and even when loud innocent murmurs may disappear in inspiration. In the absence of heart failure the Valsalva maneuver has been used to determine whether a murmur originates in the pulmonary or systemic circulation.[44] During straining, cardiac murmurs are decreased because the increased intrathoracic pressure decreases venous return, depletes the pulmonary circuit, and decreases filling of the left heart. On relaxation, venous and pulmonary arterial flow increase promptly. Increased filling of the left heart does not occur until the pulmonary circuit has been replenished. The murmurs of tricuspid incompetence and pulmonary stenosis intensify immediately on relaxation. Intensification of the murmurs of aortic stenosis, mitral incompetence, and ventricular septal defect is delayed until several cardiac cycles after relaxation.

Exercise plays no role in the differentiation of innocent from pathologic systolic murmurs.[23,44] Both may be increased, decreased, or not significantly altered by exercise.

Effect of posture

Innocent systolic murmurs are frequently influenced more by changes in posture than are organic murmurs.[4,23] The murmur of aortic stenosis when quiet may be audible only with the patient erect. The systolic component of venous hums is louder with the patient erect. It becomes soft or absent when the patient is examined in recumbency.[23] This behavior is helpful in distinguishing venous hums from continuous or systolic murmurs especially in children, pregnant women, and patients whose circulation is overactive.

Effect of pharmacologic agents

Certain pharmacologic agents modify murmurs by altering resistance to flow in the systemic or pulmonary vascular beds. Amyl nitrite lowers peripheral vascular resistance promptly and profoundly.[44] As a result, arterial pressure falls and heart rate and venous return increase.[44,46] Amyl nitrite reduces regurgitation from the left ventricle or aorta; consequently, the length and intensity of the murmurs of mitral incompetence,[44,47,48] ventricular septal defect,[44] and patent arterial duct[44] are reduced. The effects of amyl nitrite on the murmurs of tricuspid and mitral incompetence are opposite.[41,44] The increased venous return augments tricuspid incompetence and the resulting murmur.[44]

Ejection systolic murmurs are increased after inhalation of amyl nitrite.[44,47] The resulting augmented flow lengthens and intensifies both aortic and pulmonary systolic murmurs[44] (with the exception of the tetralogy of Fallot). This effect is greater in ejection murmurs caused by stenosis than in those caused by rapid flow.[44,4] This behavior helps to differentiate organic from functional or innocent murmurs.[44]

The augmented venous return that follows the inhalation of amyl nitrite raises right ventricular pressure and output and intensifies the murmur if there is pulmonary stenosis with intact ventricular septum.[44] In tetralogy of Fallot the lowered systemic vascular resistance after the administration of amyl nitrite causes more blood to cross the ventricular defect and less blood to flow through the pulmonary valve. The pulmonary ejection murmur, therefore, becomes softer and shorter.[49] By raising systemic vascular resistance in tetralogy of Fallot, phenylephrine decreases the right-to-left shunt and increases flow through

the pulmonary valve.[44] *Phenylephrine has* no significant effect on the murmur of uncomplicated pulmonary stenosis.[49] Amyl nitrite and phenylephrine have been employed to differentiate acyanotic tetralogy of Fallot from pulmonary valvular and infundibular stenosis with intact ventricular septum.[44, 49]

Serotonin causes pulmonary vascular resistance in the dog[41] and has been thought in this manner to increase tricuspid incompetence and the amplitude of the murmur in man,[46] although serotonin does not elevate pulmonary arterial pressure in man.[47] L-norepinephrine increases both systemic and pulmonary vascular resistances[41] and therefore increases the amplitude of the murmurs of both tricuspid[44] and mitral incompetence.[44, 49] Methoxamine (Vasoxyl) increases only systemic vascular resistance[50] and accentuates the murmur of mitral incompetence.[44] Mephentermine (Wyamine) has been employed to raise systemic vascular resistance in patients with patent arterial duct in whom the murmur is confined to systole.[44] The elevated systemic resistance favors increased flow from the aorta through the duct to the pulmonary artery, and the murmur may become continuous.

Innocent systolic murmurs. Frequent reference has been made to innocent systolic murmurs. So important is this class of murmur, so grave the possible consequences of its misinterpretation, that it is difficult to overstate its significance. The interpretation of innocent systolic murmurs presents a challenge to pediatricians, general practitioners, and internists. To make a confident diagnosis of a normal heart in the presence of a systolic murmur is often more difficult than to recognize the various cardiac abnormalities, even for the experienced cardiologist. A considerable proportion of the patients, especially children, referred to this center for diagnosis or special investigation have innocent systolic murmurs.

Innocent murmurs are usually soft, but may be of Grade 3 intensity.[64] They are seldom accompanied by a thrill. They may be rather musical.[23, 24, 31] The intensity and duration of innocent murmurs are often greatly modified by both respiration and position[23] and are apt to vary between examinations. The effect of exercise is inconstant[23] and does not distinguish innocent from organic systolic murmurs. Amyl nitrite only slightly increases the amplitude of innocent murmurs, as compared with organic murmurs.[45] Innocent murmurs are very common in children and are frequently present in young adults.[46] In one study innocent systolic murmurs were found in 23 per cent of 500 schoolchildren,[66] and in another study of 5,541 students between the ages of 12 and 19, innocent systolic murmurs were heard in 37 per cent of the boys and 51 per cent of the girls.[67] In young adults, they are a frequent cause of difficulty during examinations for employment, induction into the Armed Services, and eligibility for life insurance. Subjects with innocent systolic murmurs are often thought to have a ventricular septal defect or rheumatic mitral incompetence. Innocent systolic murmurs are found in healthy subjects with normal hearts, and functional systolic murmurs are heard when the heart is structurally normal but the circulation is rapid. The distinction between innocent and functional systolic murmurs cannot always be made, and many authors use the terms interchangeably.

Innocent systolic murmurs are of three main types: short apical systolic murmurs, basal ejection murmurs, and late systolic murmurs.[23, 24] Intracardiac phonocardiography in normal subjects discloses soft ejection vibrations in the pulmonary artery.[68, 69] A slight exaggeration of these normal vibrations would render them clinically audible.[70] This is the probable explanation of innocent pulmonary systolic murmurs and of functional systolic murmurs associated with physiologic increase in cardiac output, as with exercise, excitement, and pregnancy. The same explanation holds for the systolic murmur found in fever, thyrotoxicosis, anemia, and other causes of a high output state. These murmurs are followed by a normal second heart sound, which distinguishes them from the murmurs of significant atrial septal defect or pulmonary stenosis. The recognition of minute atrial defects and minimal pulmonary stenosis is virtually impossible with clinical and standard laboratory procedures.

An ejection murmur may often be audible at the apex or lower left sternal border in children.[32] It is frequently very short and the silent intervals between it and each heart sound are readily appreciated. The crescendo is early. These murmurs are intensified by amyl nitrite.[34]

Late systolic murmurs are common in children and young adults. Such murmurs are sometimes initiated by a late systolic click and are usually low pitched.[34] Numerous patients with late systolic murmurs have been referred to this center with a diagnosis of mitral stenosis because the murmur had been confused with a presystolic murmur. This error is avoided when the examiner takes care to identify the first heart sound. Minimal mitral regurgitation could conceivably be confined to late systole and produce a late systolic murmur.[34] It has been maintained that in such cases phonocardiography records minimal early vibrations that are not audible clinically.[41] A very short left parasternal systolic murmur may rarely be caused by a minute muscular ventricular septal defect which closes during the latter period of systole but the vast majority of such murmurs are considered to be innocent.[34,41] It must be emphasized that in the present state of knowledge much more harm is done when an innocent systolic murmur is mistaken for evidence of heart disease than when an insignificant lesion is missed.

Summary

The mechanism of systolic murmurs is poorly understood. Murmurs occur when flow is turbulent, but they are not necessarily caused by the turbulence. Cavitation is considered to be an unlikely explanation for murmurs. Irregularities of endocardium and endothelium may set up vibrations analogous to Aeolian tones.

The location and transmission of murmurs may be atypical. The murmurs of aortic stenosis and tricuspid incompetence, which are best heard at the apex, are good examples. The over-all quality of a murmur is frequently distinctive. The classification of systolic murmurs into (1) pansystolic murmurs caused by regurgitation from a ventricle to an atrium or across a ventricular septal defect, and (2) ejection murmurs caused by actual or relative semilunar valve stenosis is helpful in the recognition of individual murmurs. Further classification of nonpansystolic murmurs into ejection murmurs and short early, mid and late systolic murmurs avoids the over-simplification of recognizing only two types of systolic murmurs when in fact there are several. These classifications relate systolic murmurs to their pathophysiology. Inspiratory increase in systolic murmurs from the right heart, and the greater effect of respiration on innocent murmurs than on organic murmurs are useful diagnostic aids.

Pharmacologic agents which alter the peripheral or systemic vascular resistance may be employed to separate ejection from pansystolic murmurs. These agents also help to decide whether a murmur originates from the right or left side of the heart. Amyl nitrite and phenylephrine have been used to settle the diagnosis between pulmonary stenosis and tetralogy of Fallot.

Innocent systolic murmurs are common. Their quality, timing, and variation with respiration and posture are often characteristic. In some instances their interpretation is difficult even after detailed cardiovascular studies. In general, more harm is apt to result from misinterpretation of an innocent systolic murmur than from missing an insignificant organic lesion.

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Evaluation of dipyridamole (Persantin)

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In 1951 a new double-ring structure was formed from two condensed pyrimidine rings, and several chemical compounds were made using the new basic structure. One of these compounds when tested pharmacologically in animals was found to have a selective effect on coronary vessels producing dilatation and increased coronary blood flow without significant changes in heart rate or blood pressure or significant effect on peripheral vessels when used within a limited dosage range. It was also found to be quite effective in counteracting the coronary vasoconstriction induced by the administration of Pitressin. Subsequently this compound originally given the code letters *RA-8* received the nonproprietary name *dipyridamole*. It was promptly recognized that this drug might be useful clinically. Additional work, particularly in dogs, confirmed the fact that this drug was indeed a powerful coronary vasodilator. Coronary blood flow increased considerably with an intravenous dose of 0.5 mg. per kilogram. There was also an increase in coronary sinus oxygen. In dogs in which coronary artery insufficiency was produced by partial ligation of a coronary artery or narrowing of the lumen by application of casein rings, there was also some increase in coronary flow but considerably less than in normal dogs. Coronary arteriography in dogs did not demonstrate significant increase in the diameter of the major coronary vessels but increased opacification of the finer tributaries was noted which suggested increased vascularization. There is also a suggestion that dipyridamole has a direct effect on the metabolism of cardiac muscle, in that it has produced an increase in adenosine triphosphate in the myocardium in the presence of anoxia. There is also some evidence that this drug has an effect on nucleoside metabolism in the heart.

Because of the excellent results of these animal experiments, clinical evaluation programs were started in many centers both in this country and abroad. In cardiac catheterization studies in human beings, with the catheter well within the coronary sinus, it was soon established that in individuals with no coronary atherosclerosis an increase in oxygen saturation of coronary sinus blood resulted (+7 per cent to +36 per cent) when doses of dipyridamole 0.16 to 0.30 mg. per kilogram were injected intravenously. These results have been confirmed by several investigators. Separate measurements have shown an increased coronary flow as well.

It was anticipated that a drug which has the pharmacologic properties described above might be very useful in the treatment of coronary artery disease, particularly when angina pectoris is present. Actual clinical results, however, are rather disappointing. Although the clinical papers in the European literature seem to indicate that dipyridamole is of value in the t

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ment of angina pectoris the well-controlled studies published in Britain and in the United States are not so optimistic. Several double-blind studies in different dosage ranges have failed to show any advantage of dipyridamole over a placebo In stress tests this drug failed to protect against changes in the electrocardiogram whereas nitroglycerin did The drug has also been tried intravenously in cases of acute myocardial infarction without any appreciable benefit being noted

Here then is a drug which has been shown in animals and in man to have a powerful dilating effect on the coronary arteries, but which appears to be of little or no value in the treatment of angina pectoris. Perhaps the fault lies in our placid acceptance as a fact rather than as hypothesis that angina pectoris is due to coronary artery vasoconstriction resulting in myocardial ischemia rather than to some other cause. One of the investigators who compared dipyridamole with nitroglycerin commented that the beneficial effect of nitroglycerin is probably not the result of coronary vasodilation at all and that some other mechanism must be considered to be the cause.

Dipyridamole in spite of its poor showing in the treatment of angina pectoris, is still a very interesting drug Further work on its metabolic effect on heart muscle is required. It is possible that this drug might conceivably be useful in myocardial insufficiency In heart failure it has been noted that after 30 mg of the drug was injected intravenously blood levels of pyruvic acid decreased to normal or near normal

The side effects which result from doses of 25 mg three times a day are slight and are usually manifested as mild gastrointestinal distress, dizziness, weakness, or nausea. Larger doses may cause peripheral vasodilatation with syncope and other manifestations of hypotension.

Carcinoid syndrome. Effective symptomatic treatment

The medical treatment of the carcinoid syndrome has almost always been ineffective. Therapy has been based on the assumption that the presenting clinical symptoms result from release of serotonin into the blood stream. This concept, however seems to represent an oversimplification, as Peart and associates[1] have recently stated. Other substances besides 5-hydroxytryptamine are probably formed in excess in patients suffering from the carcinoid syndrome these account at least in part, for some of the symptoms Although the literature includes reports of improvement with various substances which act as serotonin antagonists, no drug is known at the present time to be consistently beneficial

The two most disturbing symptoms for the carcinoid patient are the diarrhea and the flushes In a 58-year-old patient with the carcinoid syndrome, 1 methyl-D-lysergic acid butanolamide tartrate (UML 491 as Deseril, of Sandoz)[2] and of 1-[p-dimethylamino-benzyl]-2[5-methyl-3-isoxazolyl-carbonyl]-hydrazine (Ro 5-1025 of Hoffmann-La Roche) were observed to alleviate these symptoms consistently

He had suffered from shortness of breath and diarrhea for 5 years. In 1958 he began to have attacks of facial flushing 2 years later they were of daily occurrence In 1959 diarrhea became resistant to the usual therapy The 24-hour urinary output of 5-hydroxyindole acetic acid varied between 143 and 674 mg (normal upper limit 10 mg.). Radiologic investigations revealed the site of the primary neoplasm to be in the ileum. At necropsy in September 1961 three small carcinoid tumors were discovered in the upper part of the ileum, and two large metastases in the liver

In December 1960 when Deseril was given orally up to 6 mg per day watery bowel movements stopped and were reduced to one formed movement daily Diarrhea returned when the drug was stopped but it was controlled again when treatment was restarted. However the flushes were not influenced by this therapy The addition of Ro 5-1025 orally 20 to 75 mg. per day decreased and shortened the duration of the very intense and annoying flushes. When Ro 5-1025 was stopped flushing recurred promptly With the combination of the two drugs the patient was kept relatively comfortable and was able to work half day for several months up to 1 month before his death, which was due to heart failure of the right and left sides.

In this case the administration of Deseril and Ro 5-1025 clearly alleviated the diarrhea and the flushes, although we were unable to explain their action. Peart and Robertson[4] reported on the effect of Deseril in 3 patients who responded favorably in regard to diarrhea. In one patient, large doses of Deseril (36 mg. a day orally) given alone, had an inhibitory effect on the flushes of the severe type. In a female patient (born 1913) with the carcinoid disease whom we have had under our observation, we were able to stop instantaneously a similar violent attack of flushing, accompanied by severe dyspnea and nausea, by the intravenous application of Deseril (0.5 mg). Laur[3] has reported a case of carcinoid disease in which Deseril relieved the diarrhea but had no effect on the other features. Schaeckloth and associates stated that little or no benefit was seen.

The action of a new monoamine-oxidase inhibitor Ro 5-1025 which at the same time inhibits amino-decarboxylase, seems to be of particular interest, but has, to our knowledge, not yet been tested in patients with the carcinoid syndrome. When Ro-5-1025 was given in combination with Deseril, a definite reduction in the number of flushes and their duration was observed in our patient. No hypotension or other adverse side effects occurred with the two drugs.

Another substance, α-methyl-3-4-dihydroxy-D-L-phenylalanine (M K. 351, N C-2294, Merck Sharp and Dohme, Rahway N J), showed definite suppression of the flushes in our patient without affecting the diarrhea. However this latter serotonin antagonist caused alarming side effects in the psychic behavior of the patient, necessitating discontinuance of the drug

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Immunologic relationship of group A streptococcal strains and human heart tissue. Possible significance for the pathogenesis of rheumatic fever

It is well established that attacks of rheumatic fever are related to antecedent streptococcal infection. The nature of the pathologic process involved is unknown, although most authorities have been attracted by hypotheses which embrace an immunologic mechanism. In recent studies attention has been directed to the role of autoimmunity. Earlier reports in the literature described reactions of rheumatic sera with extracts of heart by complement fixation and collodion particle agglutination[1-3] and more recent observations have employed antiglobulin consumption and immunofluorescence.[4,5] However, the significance of these presumed autoimmune factors, whether of pathogenetic importance or whether representative of nonspecific response to tissue inflammation, could not be assessed. Most studies indicated that these serologic factors were not specific for rheumatic fever.[1-3] Immunologic specificity of such reactions was undetermined, although some evidence of heterogeneity of reactive properties was suggested.

Immunofluorescent studies in this field offered new approaches to the problem. In direct studies of rheumatic heart tissue obtained at surgical biopsy or postmortem, evidence was obtained of a characteristic deposition of bound gamma globulin in myofibers and vessel walls. These deposits were characteristically associated with evidences of histochemical alteration, namely, metachromasia with toluidine blue, increased reactivity with the PAS stain, and increased affinity for eosin—changes associated with fibrinoid degeneration. In one patient widespread deposits of bound gamma globulin, observed in ventricular myocardium at postmortem, were believed to be related to the unremitting cardiac failure exhibited clinically. As determined by immunofluorescence, the sera of many patients with rheumatic fever and rheumatic heart disease exhibited serologic activity with heart tissue, notably with constituents of cardiac myofibers, and less frequently with components of vessel walls and connective tissue. It was considered probable that the deposits of bound gamma globulin observed in rheumatic hearts were derived from circulating autoimmune bodies, although direct evidence of this could not be obtained.

These observations, suggesting the participation of an autoimmune mechanism in the pathogenesis of rheumatic fever, offered no clue as to the possible role of the group A streptococcus. Among various hypotheses considered was the concept that such an autoimmune mechanism might be initiated by an antigen in the group A streptococcus which was immunologically cross-reactive with human heart tissue. This concept was put to test by determining whether rabbits immunized with group A streptococcal cells exhibited serologic cross-reaction with human heart tissue. It was found that rabbits immunized with the isolated cell walls of group A, type 5, streptococcus, originally isolated from the throat of a patient with acute rheumatic fever, developed serologic reactivity with human heart by immunofluorescence and by complement fixation. The reactant in the heart was localized to cardiac myofibers and to smooth muscle cells of vessel walls and endocardium. This serologic reaction could be specifically absorbed with isolated cell walls of this streptococcal strain and with acid extracts of the cell walls. In subsequent purification studies this cross-reactive antigen was found to be closely associated with M protein, the factor related to the virulence of the group A streptococcus.

Thus, these data have given evidence of antigenic material in group A streptococcal cell walls of cer

tala strains, probably protein in nature, which is immunologically related to constituents of human heart tissue. Thus far this cross-reactiv antigen has been found in four type 5 and in four type 19 strains, but not in several other strains of groups A, C D and G. These observations are consistent with the concept that the bound gamma globulin in myofibers and in vessel walls in rheumatic hearts is related to antibodies reactiv w th antigen in these sites, and that such an immune mechanism may be responsible for the myocarditis and arteritis observed in rheumatic fever. According to such a view it might be considered that exposure to the group A streptococcus in the susceptible, and presumably hyperresponsive, individual results in induction of utoantibodies to heart, th deposition of gamma globulin in the heart. I certain individuals such an utoimmune mechanism might be self-perpetuating, with resultant chronicity of the disease process.

As yet, relationship of autoantibodies to heart to other stigmata of rheumatic heart disease such as the Aschoff lesion, valvular deformity subcutaneous nodules, or chorea, is not clear. It remains to be determined whether the tissue and humoral distribution of this cross-reactive antigen and the type of autoimmune response i.e., whether related to circulating antibody cell-fixed antibody or antigen-antibody complexes, have relevance for the nature nd distribution of these arious lesions.

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Deterioration after mitral valvotomy

Many patient with mitral stenosis are greatly improved by surgical treatment because widening of the valve orifice and, in arying degree, the restoration of mobility to the cusps result in fall in intrapulmonary pressures. Symptoms may be relieved but it is known that after al otomy the pulmonary arterial and enous pressures, and in particular the pulmonary ascular resistance, usually remain elevated, especially on exercise. Often the cardiac output changes less than might be expected nd the right entricle continues to pump against an elevated resistance.

The number of patients who deteriorate increases year by year I some this is due to re-fusion of the cusps, and in others to progressive sclerosis and rigidity of the val e, resulting in functional stenosis. Deterioration may be associated with ingle dominant factor such as traumatic (operativ) mitral incompetence, or is attributable to multiple ad erse factors which can be grouped under the general heading of progress in the natural history of rheu matic carditis, although often such activity can only be suspected. In some patients, deterioration or limitation in the degree of improvement is due to related disease in the lungs or elsewhere, and sometimes to psychological factors. Occasionally deterioration is precipitated by respiratory infec tion, pulmonary infarction pregnancy or bacterial endocarditis.

W ha recently analysed the records of the first 500 patients from the cardiac department of the Western General Hospital in Edinburgh who ha

been treated by valvotomy *for pure tight mitral stenosis* during the past 11 years and more than 12 months ago. The valve orifice accepted less than the terminal phalanx of the index finger in 480 cases (96 per cent), and just admitted the terminal phalanx in the remainder. We have been less concerned with those who have maintained good functional result than with the general problem of those who subsequently deteriorated after operation.

The series is uniform in that, as previously described, all patients were admitted to the same medical ward and were assessed in a similar manner by three of the same four observers, and almost all were operated on by the same surgeon (Mr. Andrew Logan). Postoperative results were divided into three groups: "Good," "fair," and "poor." "Good" implied great functional improvement with the ability to carry out normal housework or previous occupation. "Fair" implied considerable improvement but with some dyspnea on moderate exercise and usually the necessity for some home help or an occupation involving little physical exertion. "Poor" implied slight or no improvement or actual deterioration due to the operation, such as from traumatic mitral incompetence or systemic embolism.

From the beginning we have offered the prospect of surgical relief to many severely disabled patients with tight stenosis despite relative contraindications, including an age over 50, considerable cardiac enlargement, heavy calcification of the valve, or aortic valvular disease, and appreciate that these might be regarded as absolute contraindications in centers in which different criteria are adopted. Undoubtedly a few patients have died as a direct result of this policy when otherwise they might have lived their restricted lives for a longer period. However in this group there has been a large proportion of worth-while results and, on balance, we believe that our policy as regards the selection of cases for operation has been justified by the results.

Over an 11 year period the operative mortality has remained almost constant at 6 per cent, despite a high incidence of important complicating features before operation. Since the risk in the individual case cannot reasonably be assessed from the over-all analysis of a large complex group, each potentially adverse feature has been considered separately. Systemic embolism continues to be the chief unpredictable hazard of mitral valvotomy and accounted for 13 of the 31 deaths in the whole series. Traumatic (operative) mitral incompetence was the cause of death in 6 cases. Postoperative circulatory failure occurred in 5 cases. This is likely to develop in advanced cases with myocardial damage, as reflected in large hearts, peripheral edema, and cardiac cirrhosis of the liver. Cardiac arrest occurred in 2 cases, and hemorrhage in 3 cases, but these complications are now rare.

In the first postoperative year 84 per cent of those who survived the procedure maintained a good result. At the end of 5 years this proportion fell to 72 per cent. Thereafter the rate of deterioration increased by about 10 per cent per annum. At the end of 8 years, only 42 per cent had maintained a good result uninterruptedly and of the relatively few (37) who were followed for 9 years only 20 per cent.

The incidence of restenosis steadily increased year by year and the proportion of those at risk who have required a second valvotomy rose from 5 per cent at the end of 5 years to 40 per cent at the end of 7 years, and to 70 per cent in the relatively small number who were followed for 9 years. The average interval between operations (the first of which were all carried out by finger and knife alone) was 6 to 7 years. No close relationship was found between the extent of the original operation or calcification of the valve and the incidence of restenosis. The mortality for second operations in 92 cases has been 2.4 per cent, but although so far the results of the second operation appear to be less good than those of the first, the follow-up period is too short to draw a fair comparison.

Atrial fibrillation was present in 197 cases (39 per cent), and is itself an adverse factor because of a much higher operative mortality mainly due to the incidence of systemic embolism. The effect of fibrillation on long-term results cannot yet be assessed because the total number of those who did not also have other adverse factors is too small.

Fifty-seven patients were 50 years old or older but only 7 of these did not also have fibrillation, large heart, or calcification of the valve. The numbers, therefore, are too small for any conclusions to be drawn on the significance of age itself.

Heavy calcification of the mitral valve was present in 92 patients (18 per cent). Calcification itself does not increase the operative risk, which is high only because of associated adverse factors, nor is there a higher incidence of traumatic mitral incompetence, but calcification is probably related to a higher incidence of systemic embolism. Good long-term results are fewer and are maintained for a shorter time, but the majority of patients are improved for several years, and it is clear that surgical treatment should never be refused on account of calcification alone.

A cardiothoracic ratio of 60 per cent or more was present in 111 cases (22 per cent) and is thought to reflect myocardial damage. This itself is not responsible for a higher operative mortality. Long-term results will probably be poorer, but a larger number of patients who do not also have other adverse factors must be followed to be sure of the adverse effect of enlargement itself.

The physical signs of associated aortic incompetence were present in 262 patients, and of aortic stenosis in 103 patients. Aortic valvular defects did not affect operative mortality or long-term results up to 6 years. When the degree of stenosis was severe, aortic valvotomy was carried out at the same time.

A group of patients with severe mitral stenosis but with multiple adverse features was analyzed separately. Inevitably the operative risk was greater (approximately 20 per cent) and the prospects of obtaining a good result were poorer, but the majority maintained worth-while improvement for some years. A subgroup with considerable cardiac enlargement, recurrent congestive failure, and atrial fibrillation were thought to have important myocardial damage and fared less well.

Some degree of traumatic (operative) mitral incompetence, as judged by auscultation, was produced in 97 cases (20 per cent). In 72 of these there was nothing to suggest that the systolic murmur

reflected mitral incompetence of dynamic significance. In 14 patients (2.8 per cent of the whole series) it is thought that the incompetence produced was responsible for death or for subsequent deterioration, and in another 11 (2.2 per cent) it was possible contributory cause but other adverse factors were also present which could be responsible. Since the introduction of the transventricular dilator there has been higher incidence of systolic murmurs produced but not of traumatic incompetence of dynamic significance.

Clot was present in 107 of the 500 patients, and systemic embolism occurred in 20 per cent of those with clot. Clot was most likely to be present in those *with trial fibrillation, large hearts, calcified valves,* and relatively advanced years. Embolism with sinus rhythm was rare but occurred in 10 per cent of all those with atrial fibrillation.

Our experience ppears to differ in some respects from the findings published on other series, in that *mitral deterioration and long-term results do not* accord closely with the surgeon report as regards the extent of valvotomy. These findings are surprising, but in whatever way the results are analyzed the conclusion is the same.

Frank rheumatic fever developing between operations has been rare in our series, but low-grade activity has been strongly suspected in about 15 per cent of the cases. W have suspected its presence *when in the absence of evidence for restenosis or f ... or increasing disease* of other valves or some other factor such as anemia or respiratory infection, there is general deterioration in the form of fatigue, malaise, dyspnea, increasing cardiac enlargement, or congestive cardiac failure, particularly when such manifestations persist for few months and then clear up. A elevated sedimentation rate is sometimes, but not usually present.

Significant mitral incompetence (as judged by physical signs), whether pre-existing or surgically produced, was associated with poorer results, but, although obviously an ndesirable feature, it is evident that many do ell in spite of it.

As regards the four associated potentially adverse factors—atrial fibrillation, considerable cardiac enlargement, heavy calcification of the val e, and age 50 or over—probably none would consider the first of these to be contraindication to operation, but many patients have been turned down on account of the second, third, and fourth. Yet our analysis shows that trial fibrillation is by far the most important of the four as regards the operative risk.

This analysis clearly demonstrated that, although surgical treatment may produce an important reduction in valvular obstruction, improvement is often only temporary. I most cases, rheumatic heart disease shows relentless progression, whether *from activity of the rheumatic process or from the* progressive fibrosis and sclerosis which follows activity. Also, it is evident that the rate of deterioration after initial good results is not steady but rather tends to increase steeply after 5 to 6 years. Time—that is to say the duration of follow-up—is, therefore, ery important factor in assessing results.

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Predominance of German shepherd and boxer breeds among dogs with congenital subaortic stenosis

I continuing study of spontaneous cardiovascular disease in dogs, the first cases of subaortic stenosis resulting from subvalvular fibrous connecting tissue ring were observed in 1952, and mention of the occurrence of this lesion as recorded in 1955. Clinical features of the disease were described in 1959. Earlier reports of this malformation in the dog have not been found in the literature, although it has undoubtedly been observed by others.

Since 1952 22 dogs with this congenital anomaly have been observed among total of 171 dogs with congenital cardiovascular disease. Of these, 9 were German shepherds, 10 were boxers, and the other 3 were an English bull, Newfoundland, and fox terrier. In survey for the prevalence of heart disease in 5,000 dogs examined consecutively as they ppeared in the clinic, German shepherds made p 5.4 per cent and boxers 8.2 per cent of the total sam

ple. The prevalence ratio of congenital heart disease among the 5,000 dogs was 5.0 per 1,000 (excluding referred cases). Of the total of 25 dogs with congenital cardiac malformations in this group 3 had subaortic stenosis.

Among the 22 dogs with this anomaly 14 are known to have died or been destroyed. Of 8 which died naturally 4 dropped dead unexpectedly and 4 died of congestive heart failure. Ventricular ectopic beats are a common finding in these cases, and the speculation is that those which died unexpectedly developed a fatal cardiac arrhythmia. In the myocardium of the dogs necropsied areas of focal necrosis and fibrosis and arteriosclerosis of the small intramural arteries were found. Presumably these lesions account for the ventricular ectopic beats and sudden death. It seems likely that the myocardial and vascular changes are the result of interference with coronary blood flow because of the high intramural tension in the left ventricular wall during systole and the relatively low aortic pressure. In 5 dogs in which cardiac catheterization was performed pressure gradients across the left ventricular outflow tract ranged from 30 to over 200 mm. Hg.

Emsbo[3] and Van Nie[4] have each described subaortic stenosis as a fairly common congenital cardiac malformation in swine on the basis of a study of slaughterhouse material.

This aggregation of two breeds of dogs in a series of 22 with congenital subaortic stenosis suggests an hereditary etiology even though it is evident that the malformation occurs only sporadically (see Haring and Lewis[5]).

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Book reviews

A Surgeon's Guide to Cardiac Diagnosis. Part I The Diagnostic Approach. By Donald N Ross, B.Sc. M.B., Ch.B F R.C.S Consultant Thoracic Surgeon, Guy Hospital, London. I troductory note by Professor R. Zenker Munich, Germany Berlin, 1962 Springer Verlag 72 pages, 86 illustrations.

This booklet, only 70 pages in length, presents a concise review of the diagnosis of surgical heart disease. The pertinent embryology is reviewed, and the pathophysiology of heart disease (particularly pulmonary hypertension) is well presented. Physical examination of patients with heart disease is discussed in detail, and newer diagnostic aids, such as cardiac catheterization and angiocardiography are well summarized.

The book has been written with exceptional clarity The illustrations, including many in color were carefully chosen, and the reproductions are outstanding The printing is of the highest quality

This book is highly recommended to medical students, surgeons, and internists who want concise review of the diagnosis of surgical heart disease.

Cerebrovascular Accidents as a Public Health Problem (Selected Recent Abstracts). Edited by Charles M. Wylie, M D Dr P H (Research in Public Health Administration Project, School of Hygiene and Public Health The Johns Hopkins University Baltimore, Md Public Health Administration, 1962 72 pages Gratis.

This is compilation of 123 abstracts of recent papers on the subjects of cerebrovascular accidents and associated problems. They ha been assembled nder four headings Epidemiology and Statistics. The Acute Phase, Diagnosis, Prognosis and Treatment The Long Term Phase, Rehabilitation, Predicting the Results and Measuring Disability Problems in Program Planning

Most of the bstracts are ery short and were obviously written with the idea of cataloguing material to encourage the reading of the original articles. The owed purpose of the booklet is to select papers that are of interest nd importance to health administrators who are developing public health programs aimed t controlling problems arising from cerebrovascular disease.

Radioisotopes in Cardiovascular Disease. Edited by Charles K Friedberg M D., and Solomon Sil er M D ith 21 contributors. New York, 1962, Grune & Stratton, Inc., 153 pages. Price $6.75

This is reprint of the May and July 1962, issues of *Progress i Cardiovascular Disease*. In addition to preface and brief glossary there are eight articles, as follows:

"The Use of Radioisotopes in Clinical Studies of the Central Circulation by E. Braunwald, A. G Morrow and R. Folse. Several isotope techniques in use at the National Heart Institut are described. These are primarily used as part of cardiac catheterization.

Blood Volume and Heart Disease by S. S. Schreiber and M A. Rothschild. Techniques for measurement of intra ascular olume are critically nalyzed, and the literature on plasma and red cell olume in heart disease is reviewed.

Determination of Cardiac Output by Means of Radioisotope Technic—With a Discussion of Central Blood Volume and Val ular Regurgitation by G. Glick, B F Schreiner M N Luria, and P N Yu. The discussion of the determination of cardiac output includes primarily the authors own experience. The remaining material includes discussion of the available literature i this rapidly developing area.

Selecti Quantitative Radiocardiography by L. Donato. This is primarily description of the difficulties which surround the obtaining of radiocardiograms selectively from the right and left ventricles in man. Although interesting, the authoritarian approach and poor labeling of figures (and inversion of one unlabeled figure) detract from the presentation. The author describes a method utilizing analogue analysis and a series of assumptions which makes it possible to make repetitive simultaneous estimates of right and left ventricular outputs, pulmonary blood olume, and other parameters. In the example given of a normal digitalized patient the raw data are not illustrated, but the summary shows that left entricular output exceeded right entricular output by pproximately 270 ml. per minute for at least 8 minutes, without change in the pulmonary blood volume, which is shown as pproximately 260 ml.

"Coronary Artery Blood Flow by G. Sevelius. This is the most recent of series of papers by the author and his co-workers dealing with quantitation of coronary blood flow by surface counting These reports have aroused a great deal of interest. Although the first publication ppeared in 1959 the results have not been duplicated. The basic problem is the recognition and quantitation of coronary peak in the radiocardiogram. Other observers have not identified this feature. The present paper contains confusing instructions nd nomogram which makes it possible to calculat coronary blood flow from the radiocardiogram nd a simultaneous curve of radioactivity in the neck, without the necessity of being able to identify coronary peak by inspection.

This series of publications by Dr Sevelius and his co-workers documents the manner in which investigators, editors, and publishers can embrace seemingly easy solution to an important problem, despite widespread objections and the failure of the work t fulfill the usual requirements for scientific publication.

"Some Factors Influencing Interpretation of

Studies of Body Water and Electrolytes with Isotopic Tracers by S. A. Threefoot This is a critical résumé of the complex problems associated with measurements of electrolyte content and behavior by dilution methods.

Treatment of Euthyroid Cardiac Patients with Radioiodine and Antithyroid Drugs by H. L. Friedell, E. L. Schoeniger and J. P. Storaasli This is a brief appraisal of the therapeutic use of radioiodine to produce myxedema in euthyroid cardiac patients with congestive failure or angina pectoris. It is based on the authors' experience in 207 patients. Favorable results were obtained in a majority.

The Treatment of Thyrocardiac Disease with Radioactive Iodine by S. Silver, C. Delit, and M. Eller This is a summary of I131 treatment series which includes 187 patients with congestive heart failure and hyperthyroidism. The recurrence rate of hyperthyroidism in cardiac patients was 1 2 per cent.

HOT CLIMATES, MAN AND HIS HEART. By George E. Burch, M.D., Henderson Professor of Medicine, Tulane University School of Medicine, and Nicholas P. DePasquale, M.D., Instructor in Medicine, Tulane University School of Medicine, New Orleans, La. Springfield, Ill., 1962, Charles C Thomas, Publisher. 196 pages. Price $10.50.

The reader of this comprehensive review of the many basic researches conducted since the early nineteen-forties in the Tropical Physiology and Cardiovascular Laboratories of the Tulane University School of Medicine under the direction of Dr. Burch on the effects of hot and humid environments on man is enjoined to read carefully the Preface. The main intention of this monograph is to present those contributions, and not to review the other available literature as a whole. It is hoped that, with the authors' vast background and experience in the subject, such a text eventually may be forthcoming.

The material is presented in a logical sequence, starting with the introduction and progressing to studies on the loss of heat and water from the skin and the lungs, the role of electrolyte excretion, and the effects of hot and humid stresses upon the peripheral, general cardiovascular and renal circulations of normal man and man with heart disease. In each chapter a clinicopathophysiologic correlation is made with the antecedent experimental data. A final chapter presents clear clinical discussions of the syndromes due to exposure to hot and humid weather.

The authors have succeeded admirably in writing a text which should have great appeal to a wide group of readers ranging from medical students to those interested experimentally and clinically in man's adaptation to climate. Because of the intended scope of this monograph, the beginner will need to acquire considerable knowledge in order to appreciate fully the experimental material; the more sophisticated reader will have to be understanding of the occasional oversimplifications in the clinical portions of the text.

ADVANCES IN RHEUMATIC FEVER. By May G. Wilson, M.D., Professor of Clinical Pediatrics, Emeritus, Cornell University Medical College, Ithaca, N. Y.; Consulting Pediatrician and Director, Rheumatic Fever Research, New York Hospital, New York, N. Y. New York, 1962, Harper and Row, Publishers. 249 pages. Price $10.

This monograph was intended as a supplement, not a revision, of a former monograph, *Rheumatic Fever*, covering the years 1916-1940. It is a summary and discussion of recent developments in the study of the disease, written by a worker long recognized for her contributions in this field. Some of Dr. Wilson's interesting, unconventional, and controversial viewpoints are expounded, i.e., short term, high-dose hormone therapy, intermittent prophylaxis, the possible pathogenetic effects of nonspecific stress.

The book is heavily weighted toward the statistical-epidemiological approach to the study of rheumatic fever and very little attention is given to newer diagnostic approaches, such as cardiac catheterization and angiocardiography in rheumatic heart disease. The advances in cardiac surgery for valvular disease are given disappointingly little consideration. The discussion on recent advances in pathology are weighted with the viewpoints of Dr. Wilson's colleague, Dr. George Murphy, and neglectful of other viewpoints. The chapter on "Diagnosis and Course" is weak in clinical fundamentals and laden with clinical protocols of dubious relevance, but gains value from Dr. Wilson's many years of documented follow-up of a large number of patients, supplying data on the natural course of the disease.

This monograph should not be considered to be a comprehensive, objective, and critical review of the recent literature on rheumatic fever. It is mainly a review and discussion of Dr. Wilson's own work and ideas, accompanied by a selectively biased review of the contemporary literature. It is recommended as interesting reading, as long as one knows what one is getting.

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Editorial

Semantics and the electrocardiographic report

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The light of Humane minds is perspicuous words, but first snuffed and purged from ambiguity
— Thomas Hobbes

The accepted fashion of presenting a scientific report is first to give the facts, second, to discuss them, and finally, to present a conclusion. In this country and abroad the electrocardiographic report follows this model quite closely. The initial part consists of a catalogue that includes the rate of the heart, the P-R interval, the QRS duration, and the rhythm, and the direction of various deflections in various leads. The length of the discussion which may follow in the report immediately after this [illegible]laboration or which may be included with the more comprehensive clinical report, varies with three factors: (1) the electrocardiographer's estimation of the sophistication of the reader of the report, (2) the loquaciousness of the reporter, and (3) the confidence of the reporter in his diagnosis. When the electrocardiographer feels quite secure in his opinion, he can express it in perhaps two or three words, but when he is uncertain it may run to a paragraph or longer. Since 15 years or so ago, for economy and simpl[illegible]tion, and from the reflection that portions of the electrocardiogram are attached for first-hand observation in any case, making description of all its details redundant, we have generally omitted the first or descriptive category from our reports. Now with automatic electrocardiographic computers presenting the threat of our extinction, the writing on the wall must be heeded and the advisability of even further condensation considered. Those who have heard the ominous voice on the hospital loudspeaker intoning the words "Paging the ECG machine!" will certainly understand. And it is perhaps inevitable that a certain amount of electrocardiographic reading may have to be abandoned to the machine. But there is still much art (in contradistinction to science) in electrocardiography. And certain semantic and syntactic niceties of language are too subtle for the electronic computer. It seems likely, therefore, that for the forseeable future there will be a place for the personal electrocardiographic report. It is the purpose of this discussion to illustrate, through example or fallacy, the discrimination which can be exercised in the wording of this report.

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A common error is the substitution of concept for fact. Depression of the RS-T segment may represent a normal variation but it can also be the effect of subendocardial ischemia, of potassium depletion or of digitalis effect. Any of these factors may be operating independently or two or more may be acting in concert. In many instances it is possible on the basis of certain criteria to separate one from the other. In a considerable number, however, this is impossible. Yet generations of interns have glibly been referring to this phenomenon as "subendocardial ischemia" rather than as "RS-T segment depression." In other words, they have been guilty of the misleading practice of presenting interpretation rather than fact. Another error is to refer to the same phenomenon with different words as if they had different meanings. Thus, the change in designation from "impure flutter" to "coarse fibrillation" is noted as if it were a meaningful change. Another error is to state that a tracing shows "rapid atrial fibrillation." This ambiguous term is generally intended to mean atrial fibrillation with a rapid ventricular rate but it may be intended to refer to the frequency of fibrillation waves.

Furthermore, there is a tendency to include superfluous information in a perfectly adequate report. If an electrocardiogram shows distinctive evidence of fresh infarction, of what earthly value can the additional implication of myocardial ischemia be? For example, if there are deep Q waves, elevated RS-T segments, and inverted T waves in Leads II, III, and aVF indicating an acute diaphragmatic myocardial infarct, and the T waves are inverted over the left precordium, the report is commonly given that the patient has an acute infarct and, in addition, shows ischemia of the anterolateral myocardial region of the heart. This is very much like telling a patient that not only does he have cancer but also, old fellow, a bad case of hangnail. Unless it really adds something to the report, such additional information could very well be omitted altogether.

Another error in semantics is to talk about the "disappearance of criteria." At one time the tracing will satisfy, say, the voltage criteria of Sokolow for left ventricular hypertrophy. In a subsequent tracing these criteria will not be satisfied. The student reports the "disappearance of the criteria." The criteria, of course, stand eternal in the heavens—or semi-eternal in the heavens! The only change is that at one time the electrocardiogram does, and at the next time it does not, satisfy these criteria. The pronounced changes in voltage which may occur from day to day may always fall within the normal range or they may vary so that at one time they do and at another time they do not satisfy the voltage criteria for hypertrophy. Every natural phenomenon must have a cause; these changes in voltage must also have a cause. Although we can recite a number of explanations for such a change, we are unable to name the single cause in a particular case, and we cannot be certain how many causes may be operating in combination. The common tendency, however, is to describe these changes from one tracing to another. Until more is known about this, it is probably wisest to consider this to be unexplained. My own preference is to regard it as unimportant and not mention it at all in the report.

It is likewise common experience that one set of tracings does not, and another set recorded a few days later does, show evidence of myocardial infarct. It is only in the QRS complex that this change is recorded; the electrocardiogram does not, at the same time, show dynamic changes in the RS-T segment or in the T wave. Between these two tracings there may or may not have been an episode which is suspected of representing actual myocardial infarction. The temptation is to regard the described electrocardiographic changes as signifying the interim development of fresh infarction. But in our experience it is not uncommon for infarction to be manifest at one time and not manifest at another. In the contingency just described it would be preferable to refer to this as an emergent change rather than a development. Thus, although it is possible that a fresh infarct has actually developed in the interim, it is also possible that one has been present all along, at first concealed and later revealed. The use

of the word "emergent" here, it seems to us, covers either possibility without committing the interpreter to one.

A few remarks on the repeat report are pertinent. In an attempt to condense what has already been said in the previous report, there is a common tendency to corrupt the original meaning by repeating as a certainty what originally had been stated as only a possibility. It should be remembered also that repetition strengthens an opinion. A possibility restated accurately as a possibility sounds like a still stronger possibility. If something has already been merely suggested and there is no further evidence supporting this possibility, it is just as well to omit reference to it in the second interpretation. This does not deny that this possibility still exists. On the other hand, if the evidence for this has become stronger, this should be so stated. And if the evidence for it has become weaker, or if there is no longer even a suspicion of it, a negative statement to this effect should be made.

Finally, it should be remembered that the words employed may sound stronger than the facts they are intended to convey. At one reading, for example, the P-R interval may be measured as 0.20 second. In a subsequent tracing this is measured as 0.21 second. This immediately changes its pigeon-hole from normal to pathological and the diagnosis of first-degree atrioventricular heart block is made. What a tremendous difference and all these words for only 0.01 second! The difference may be accounted for by a change in atrioventricular time or by a technical or personal error—by variation in paper speed, in the refractive index of the observer, or according to which side of the bed he happened to arise from that morning.

It is said that the Light Brigade charged to its doom at the Battle of Balaclava because "someone had blundered." The blunder was due to a misinterpretation of the direction "There, my Lord, is your enemy." The ambiguity in the word "There" resulted in the commander of the Light Brigade attacking the wrong Russian position. The men of the Light Brigade died because of a word. History is full of examples of men who have died in the name of words whose meaning is vague or nonexistent.

It is good to believe that the human mind is more capable of these distinctions than a mere machine.

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Electrocardiographic abnormalities associated with myotonic dystrophy

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Several of the neuromuscular disorders have been shown to affect organ systems other than skeletal muscle and the nervous system. Among these, myotonic dystrophy, pseudohypertrophic muscular dystrophy, myasthenia gravis,[3] and Friedreich's ataxia are all known to affect the heart. A high incidence of electrocardiographic abnormalities has been found in patients with myotonic dystrophy who otherwise have no clinical evidence of cardiac pathology. In 1950 De Wind and Jones[4] collected from the literature and their own observations 98 cases of myotonic dystrophy and noted that the incidence of electrocardiographic abnormalities was 62 per cent. Common among these abnormal findings were a low P wave, a prolonged P-R interval, delayed intraventricular conduction, S-T segment abnormalities, and various arrhythmias. Also, both Evans and Spillane[7] noted in their patients the frequent occurrence of left axis deviation.

Forty-seven patients with documented myotonic dystrophy have been studied by the Medical Neurology Branch of the National Institute of Neurological Diseases and Blindness. This review was undertaken to clarify the incidence and nature of the electrocardiographic abnormalities associated with myotonic dystrophy, and to determine whether clinically significant heart disease exists in these patients.

Method

The diagnosis of myotonic dystrophy was established by the following criteria: family history (the disease is strongly dominant), the classic clinical physical features (distal weakness, gonadal atrophy, early balding, cataracts), and the presence of reflex and percussion myotonia. In addition, electromyographic evidence of electrical myotonia and myopathic disease and/or histologic evidence of myopathy by muscle biopsy was present in all patients.

Forty-seven patients (32 males and 15 females) who ranged in age from 2 to 61 years satisfied the above-mentioned criteria. The hospital records of each of these were reviewed for evidence of cardiovascular signs or symptoms. A chest roentgenogram was available on each patient. One or more standard twelve-lead electrocardiograms taken when the patient was not receiving drugs known to alter myocardial conduction (e.g., procaine amide or quinine) were analyzed for each patient. The heart rate, rhythm, P wave amplitude

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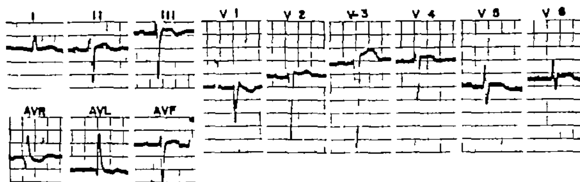


Fig. 1. Electrocardiogram of 38-year-old man, demonstrating several of the abnormalities noted in myotonic dystrophy, i.e., left axis deviation, prolonged P-R interval, and S-T segment elevation.

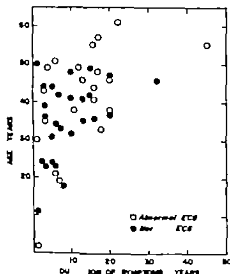


Fig. 2. Graph correlating electrocardiographic abnormalities with the age and duration of symptoms.

P-R interval, QRS duration, S-T segment elevation, and the Q-T interval were determined. The tables of Ashman and Hull were used as the normal standard. The S-T segment was considered to be abnormal if the junction was elevated from the base line more than 1.5 mm. The mean spatial vectors of both QRS and T were estimated by the method of Grant.[9] A mean QRS deviation of −30 degrees or more was defined as left axis deviation. The criteria of Sokolow and Lyon[11] were used to determine the presence of left ventricular hypertrophy.

Results

Twenty-one patients (14 males and 7 females) were found to have electrocardiographic abnormalities, as listed in Table I. Their ages ranged from 2 to 61 years. The

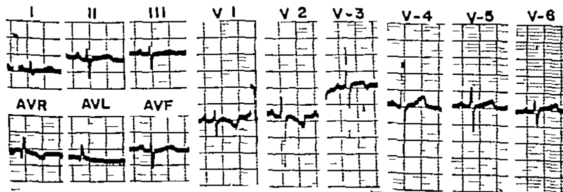


Fig. 3. Electrocardiogram of 2-year-old boy with myotonic dystrophy demonstrating left axis deviation

tracing from one of these patients with multiple electrocardiographic abnormalities is illustrated in Fig. 1. In this group 1 patient was hypertensive (Case 1), 2 had x-ray evidence of minimal cardiomegaly (Cases 1 and 13), and 1 had a history of previous myocardial infarction (Case 1) (see Table I). None of the patients gave a history of congestive heart failure or significant cardiac symptoms. Physical examinations of the heart were unremarkable in all patients except as mentioned above. No definite relation between the duration of the myotonic symptoms and the presence of electrocardiographic abnormalities was demonstrated (see Fig. 2). The electrocardiogram was abnormal in all 5 patients who were older than 51 years.

Discussion

The incidence of electrocardiographic left axis deviation in 11 of these patients (13 per cent) is unusually high. In 3 such patients the QRS duration was prolonged to 0.11 second and in 2 patients the QRS measured 0.14 second. However, in all of the patients the angle between the mean QRS and T vectors was less than 150 degrees; thus, the conduction defect did not suggest typical left bundle branch block.

In 1956 Grant[14] proposed that left axis deviation of the mean QRS vector more negative than −30 degrees denotes cardiac pathology and is due to a "parietal block" or conduction defect located in the superior branch of the left bundle. This concept has recently been supported by Samson and Bruce,[15] who noted the frequent acute onset of left axis deviation after the use of an aortic valve dilator. These authors postulated that the mechanical injury to the left bundle conduction system in the aortic outflow tract produced the conduction defect. In his pathologic correlation study of left axis deviation, Grant noted that when myocardial infarction could be excluded as the cause, the remaining hearts

Table I

Case number	Age (yr.)	Sex	Low P wave	Prolonged P-R interval	Sinus bradycardia	Abnormal S-T segment	Left axis deviation	Left ventricular hypertrophy	QRS duration (sec.)	Comment
1	61	M	✓	✓			✓		0.14	
2	30	F					✓		0.14	
3	30	M					✓		0.10	
4	37	F			✓		✓		0.08	"Low" atrial pacemaker
5	55	F					✓		0.11	
6	49	M		✓			✓		0.08	
7	49	F					✓		0.11	
8	19	F					✓		0.08	
9	2	M					✓		0.08	See Fig. 3
10	46	M					✓		0.08	
11	38	M		✓	✓	✓	✓		0.11	See Fig. 1
12	41	M				✓			0.08	Mean QRS axis −20°
13	48	M	✓	✓		✓		✓	0.07	
14	43	F		✓	✓				0.10	Mean QRS axis −20° Occasional premature atrial contractions
15	44	M						✓	0.08	
16	53	M						✓	0.10	Mean QRS axis −20°
17	51	M							0.10	Atrial fibrillation
18	38	M			✓				0.08	
19	33	F	✓		✓				0.06	
20	21	M	✓		✓				0.06	
21	46	M			✓				0.06	
Total			4	5	7	3	11	3		

demonstrated myocardial fibrosis usually related to diffuse coronary artery disease. In the present group coronary artery disease as the only cause for the left axis deviation is unlikely since 5 of these patients were under 40 years of age and 1 was only 2 years old.

Numerous possibilities could account for the conduction abnormality noted in these patients. Focal pathology of the Purkinje network, myocardial damage, biochemical changes of the muscle proteins, and physiologic alterations in the conduction properties in the cell membrane have all been suggested, but a satisfactory explanation remains to be found. Because of the strong dominant inheritance and the involvement of multiple systems, a genetically determined biochemical abnormality is currently an attractive hypothesis offered in explanation of the changes in skeletal muscle and one that also could be applied to abnormalities of cardiac muscle.

To our knowledge, no specific pathologic study of the cardiac conduction system in this disease has been published. The published descriptions of pathologic finding in hearts from patients with myotonic dystrophy have usually been nonspecific.[12-14] Fisch and Evans[15] and more recently Cannon have demonstrated a diffuse myocardial fibrosis in 2 patients with myotonic dystrophy.

Of particular interest in this group is the 2 year-old patient (Case 9) who was being screened for myotonic dystrophy because of subtle hypotonia and a positive family history. No myotonia had been found clinically and the picture was more suggestive of mental retardation than of primary muscle disease. Because of the electrocardiographic finding of left axis deviation (Fig. 3) in the absence of other evidence of congenital heart disease further studies were undertaken. A peripheral muscle biopsy revealed myopathic changes and electromyography revealed electrical myotonia. Thus, the diagnosis in the youngest patient in this group was suggested because of this electrocardiographic abnormality.

Other electrocardiographic abnormalities, i.e., low P waves, prolonged P-R intervals, were somewhat less frequent than previously reported. This discrepancy may be due in part to the use of more rigid criteria for abnormality. The incidence of arrhythmias is in agreement with findings reported by others. S-T segment elevation was noted in 3 patients. In 1 patient this finding was transient and in the other 2 it persisted. The etiology of the change in the S-T segment is unknown but it was not related clinically to acute myocardial injury.

Summary

Of 47 patients with myotonic muscular dystrophy, 21 were found to have electrocardiographic abnormalities as determined by application of standard criteria. None was found to have clinical evidence of significant heart disease which could be attributed primarily to the myotonic dystrophy. The most common finding was left axis deviation which was seen in 11 patients (23 per cent). Other less frequent findings are tabulated (Table I). The finding of left axis deviation in a 2 year-old child who had no evidence of congenital heart disease suggested the diagnosis of myotonic dystrophy.

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tracing from one of these patients with multiple electrocardiographic abnormalities is illustrated in Fig. 1. In this group 1 patient was hypertensive (Case 1), 2 had x-ray evidence of minimal cardiomegaly (Cases 1 and 13), and 1 had a history of previous myocardial infarction (Case 1) (see Table I). None of the patients gave a history of congestive heart failure or significant cardiac symptoms. Physical examinations of the heart were unremarkable in all patients, except as mentioned above. No definite relation between the duration of the myotonic symptoms and the presence of electrocardiographic abnormalities was demonstrated (see Fig. 2). The electrocardiogram was abnormal in all 5 patients who were older than 51 years.

Discussion

The incidence of electrocardiographic left axis deviation in 11 of these patients (23 per cent) is unusually high. In 3 such patients the QRS duration was prolonged to 0.11 second and in 2 patients the QRS measured 0.14 second. However, in all of the patients the angle between the mean QRS and T vectors was less than 150 degrees; thus the conduction defect did not suggest typical left bundle branch block.

In 1956 Grant[1] proposed that left axis deviation of the mean QRS vector more negative than −30 degrees denotes cardiac pathology and is due to a parietal block or conduction defect located in the superior branch of the left bundle. This concept has recently been supported by Samson and Bruce,[11] who noted the frequent acute onset of left axis deviation after the use of an aortic valve dilator. These authors postulated that the mechanical injury to the left bundle conduction system in the aortic outflow tract produced the conduction defect. In his pathologic correlation study of left axis deviation, Grant noted that when myocardial infarction could be excluded as the cause, the remaining hearts

Table I

Case number	Age (yr.)	Sex	Low P wave	Prolonged P-R interval	Sinus bradycardia	Abnormal S-T segment	Left axis deviation	Left ventricular hypertrophy	QRS duration (sec.)	Comment
1	61	M	✓	✓			✓		0.11	
2	30	F					✓		0.11	
3	30	M					✓		0.10	
4	57	F			✓		✓		0.08	"Low" atrial pacemaker
5	55	F					✓		0.11	
6	49	M		✓			✓		0.06	
7	49	F					✓		0.11	
8	19	F					✓		0.08	
9	2	M					✓		0.08	See Fig. 3
10	46	M					✓		0.08	
11	35	M		✓	✓	✓	✓		0.11	See Fig. 1
12	41	M				✓			0.08	Mean QRS axis −30°
13	48	M	✓	✓		✓		✓	0.07	
14	43	F		✓	✓				0.10	Mean QRS axis −20° Occasional premature atrial contractions
15	44	M						✓	0.08	
16	55	M						✓	0.10	Mean QRS axis −20°
17	31	M							0.10	Atrial fibrillation
18	38	M			✓				0.08	
19	33	F	✓		✓				0.06	
20	21	M	✓		✓				0.06	
21	46	M			✓				0.06	
Total			4	5	7	3	11	3		

A new disease entity
Leaflet redundancy of the mitral valve

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In the literature of anatomy and pathology there are countless descriptions of congenital variations of the human heart and great vessels.[1-4] Among these we are aware of 20 cases of duplication of the mitral valve.

This report describes the variations seen in a patient at this hospital which we believe, although it is an attempt at duplication of the valve, is not similar to those cases described and must therefore be considered a new entity. This case is particularly interesting because of the difficulty presented by the initial diagnosis.

Case report

This 11-year-old white girl was the product of full-term pregnancy and normal delivery. Initially she did well except for brief mild convulsion at the age of 3 months. A second, more severe, generalized seizure at the age of 8 months occasioned an examination by a pediatrician who discovered a cardiac murmur. When she was 1 year old, her third and final convulsion was followed by a transient episode of cardiac failure. The child was followed at 6-month intervals by pediatricians; at one time a cardiac catheterization was performed, with unknown findings. Her development had been normal and there were no cardiac symptoms except for easy fatigability.

Physical examination revealed the following findings. She was 55 inches tall and weighed 64 pounds, which placed her in the twenty-sixth percentile by height and the tenth percentile by weight, according to the development chart devised at the Children's Medical Center in Boston. The blood pressure was 80 mm. Hg systolic, 50 mm. Hg diastolic in the right arm; 90 mm. Hg systolic, 55 mm. Hg diastolic in the left arm; and 65 mm. Hg systolic, 40 mm. Hg diastolic in both lower extremities. The cardiac rate was 96 per minute with a regular sinus rhythm. A thrill was palpable over the aortic area. A Grade 4/6 systolic murmur was heard over the entire anterior chest wall, but was loudest in the aortic area and along the left sternal border. The second aortic sound was audible. The left cardiac border was enlarged to the anterior axillary line. There was no evidence of cardiac failure, nor was there any cyanosis or clubbing.

Laboratory examination revealed the urine to be normal. The hematocrit was 40 per cent, and the hemoglobin was 13.2 Gm. per cent. The erythrocyte sedimentation rate and the leukocyte count were normal. The tests for C-reactive protein and antistreptolysin O titer were negative. Serial electrocardiograms had shown progressive left ventricular hypertrophy and strain pattern, with suggested left atrial enlargement. The chest roentgenogram showed left ventricular enlargement to the lateral chest wall, a full left atrium, and increased pulmonary vascularity (Fig. 1). Cardiac catheterization was carried out on Sept. 8, 1960. There was no evidence of intracardiac shunt. Femoral arterial oxygen saturation was 94.5 per cent. Right ventricular pres-

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Fig. 1 Roentgenogram of the patient chest. There is enlargement of the left entricle to the lateral chest wall. f ll left trium and increased pulmonar asculanty

sures of 40/0 nd 36/2 mm. Hg were recorded with pulmonary arterial pressure of 25/12 mm. Hg and mean pressure of 18 mm Hg Simultaneous left entricular and femoral arterial punctures revealed pressures of 150/13 and 80/60 mm Hg, respecti ely The character of the arterial cur was not characteristic of lvular aortic stenosis, nd a diagnosis of probable congenital subaortic stenosis was made.

On Feb. 15 1961 operation to correct the defect was carried out via midline sternotomy employing cardiopulmonary bypass and general hypothermia down to 17° C. by means of a heat exchanger in the extracorporeal circuit. The total perfusion time as 46 min tes. After the usual cannulations of the right side of the heart had been carried out, bypass instituted, and the temperature partially lowered an aortotomy was performed. One ommussure of the aortic alv was nderdeveloped, rendering the h bicuspid but w thout stenosis. About 1 cm. proximal to the alve dense fibrous constricting band was palpable, a portion of which formed web. This was cut way until an index finger could be passed through this area with ease

Immediately after operation left pneumothorax was detected nd corrected using closed thoracotomy with nderwater seal drainage. For the next 24 hours the patient pulse remained between 100 and 120. After being clear initially the urine became transiently pink, with microscopic hematuria during the evening of the day of operation. The specific gra ty was 1 050, which was ttributed t the dextran of low molecular weight that the patient had received. The blood pH nd electrolytes ere normal the next morning, but tachypnea of 62 per minute was present.

The patient became questionably cyanotic, and the tachycardia became more pronounced, to 150 per minute, during the first postoperative day N evidence of cardiac failure was present, and the central enous pressure was normal. Because of electrocardiographic evidence of a supra entricular tachycardia digitalization was instituted. Her ppearance thereafter improved and the v tal signs remained table.

On the second postoperative day the child de eloped evidence of digitalis l toxication this cleared by the third postoperative day

On the following day the child developed slight cyanosis nd signs of mild cardiac failure. I spite of assisted respiration nd oxygen (which the patient had been recei ing during most of the postoperati period) her respirations became more labored, and she died abruptly on the fourth postoperati day

Descripti of heart. At postmortem examination, both pleural ca ties contained small amounts of serosanguineous fluid. The lungs together weighed 440 grams and exhibited moderate pulmonary edema and l tense pass e congestion The liver spleen and adrenal glands also exhibited moderately severe pass congestion. A horseshoe-kidney anomaly was present.

The heart weighed 350 grams, nd its contour was that of left trial dilatation and both right and left entricular hypertrophy The tricuspid and pulmonic alves were normal. The aortic valve was demonstrated to be bicuspid with fusion of the right and left posterior cusps. The corresponding



Fig. Formal n-fixed heart with ew through later l incision of left entricle. Note redundancy of anterior leaflet of mitral al and degree of hypertrophy of myocardium nd trabeculae carneae. The stick probe indicates aortic outflow tract.



Fig. 3. Collapsed, sac-like deformity of anterior leaflet of mitral valve appearing rigid and wrinkled in its fixed state.

sinus of Valsalva was enlarged and although the coronary vessels were normal in development and distribution, their ostia were dilated. Multiple mi- te fenestrations were present in the cusps of the aortic valve. Several filmy tags of translucent tissue were present on the surface of the aortic vestibule, representing remnant of the subaortic band which had been removed surgically. The circumferences of the valves were as follows: tricuspid 8.2 cm. pulmonic 5.0 cm. mitral, 8.0 cm. and aortic 5.0 cm. The right ventricular wall was 0.9 cm. in thickness, and the left ventricular wall was maximum of 2.0 cm. in thickness. The trabeculae carneae were prominent and the papillary muscles were hypertrophic.

The most significant abnormality of the heart involved the anterior (aortic) leaflet of the mitral valve. A large pouch-like redundancy of the leaflet protruded from the ventricular surface was filled with postmortem clotted blood, and was 3.0 cm. in length by 2.5 cm. in greatest diameter. Two slit-like fenestrations into the sac from the atrial surface of the valve, as well as a single, small opening from the ventricular side were demonstrated (Figs. 2, 3 and 4). These openings allowed the structure to be emptied of blood during systole but were not large enough to permit any significant regurgitation. The chordae tendineae were attached distal to the redundancy. The internal surfaces of the sac were smooth. Three other much smaller sac-like structures were present near the closing edges of the same leaflet.

Microscopic examination of sections of myocardium revealed hypertrophic fibers, enlarged and irregular nuclei and fatty degenerative changes. Sections from the apex disclosed patchy interstitial fibrosis and a few focal areas of acute myocardial ischemic necrosis, as manifested by coarse, granular fragmentation of sarcoplasm and loss of striations. Sections of the wall of the redundancy demonstrated an orderly layering of dense ground plate connective tissue which was thicker than, but otherwise similar to, the normal structure of the mitral valve. Ill-defined central areas of degeneration of basophilic fibrillary connective tissue were present, but there was no evidence of inflammation and both the outer and inner surfaces exhibited endothelial lining.

Comment

In view of the pedunculated nature of this sac like structure it is postulated that perhaps, the surgical opening of the subaortic ring with unobstructed flow enabled the anomaly to subluxate into the aortic outflow tract producing a partial obstruction. This might even have been of the ball valve type. It is equally possible that during systole closure of the atrioventricular valves would have displaced the structure into the left ventricle. Being soft and easily pushed aside when approached through the aortic valve during operation it was not apparent ante mortem.

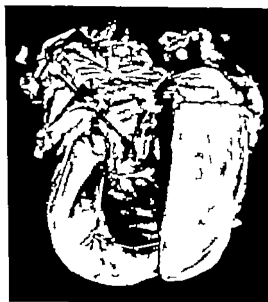


Fig. 4. Two probes entering slit-like openings on atrial surface of deformed mitral valve leaflet.

The exact nature of this structure is unknown Although it is similar to that of some cases reported we do not believe that this anomaly falls into the category of mitral reduplication In 1948 Wimsatt and Lewis summarized in a definitive paper the data which support the developmental basis for this anomaly In their paper comparison is drawn between a mitral reduplication in a ak calf and the cases reported in human beings. It is interesting that these authors came to two separate conclusions. Wimsatt believed that the double mitral orifice resulted from a subdivision of the mitral ostium through a mediolateral fusion of the mitral cusp primordia. Lewis thought that retention of the left portion of the single atrioventricular canal with consequent reduction of the mitral ostium and alignment with it resulted in the anomaly although he also conceded that it might result from a mediolateral fusion.

As might be expected from either of these descriptions and as further stated by Wimsatt and Lewis both ostia are guarded by well-defined valve cusps This is true of 17 of the 20 reported cases. Abbott[7] does not mention any valves related to the smaller ostium of the Harvard specimen Marckwald sa s that bounding the smaller ost um of his specimen there was a thickened ridge to which tendon fibers were attached This was true also of the larger orifice of Prior s triplication.

A characteristic evident in all cases adequately described has been the relation of the papillary muscles to the valve cusps. Both cusps of the ventrally situated ostium have been supplied by the ventral papillary muscle and both cusps of the dorsal ostium have been supplied by the dorsal muscle. Again Abbot does not describe such findings for her Harvard specimen but states that the ?-cm. opening in the anterior leaflet of the mitral valve led into an aneurysmal pouch which communicated with the ventricular cavity through numerous fenestrations.

In 11 of the 20 cases reported in human beings, one of the two ostia is smaller and in 9 of these it lies anterior or ventral to the larger opening [7,1] [11]Indeed some observers have described the smaller ostium simply as an opening in one of the cusps of the mitral valve. However in each of these instances with the exception of one of the cases described by Abbott, this accessory ostium has been associated with chordae tendineae and papillary muscles. It is this feature, therefore which we think is essential to the diagnosis of duplication of the mitral valve, and it is the absence of these structures in our specimen which we believe does not allow it to be included in this category of anatomic variation. Moreover it is conceivable that the Harvard specimen described by Abbott[7] in 1927 does not belong in this category for the same reasons.

Redundancy of the mitral valve is not listed in the larger series of congenital cardiac anomalies.[11] Neither is it listed as a cause of valvular stenosis, although Spencer and associates,[4] in 1960 described a pouch like diverticulum on the aortic leaflet of the mitral valve in a patient operated on for aortic stenosis which was believed to be due to "muscular hypertrophy of the left ventricle." This was so mobile that it was thought to be displaced toward the left ventricle during systole and therefore was thought not to be a contributing factor in the disease.

Edwards alluded to a similar case in 1954 in which accessory valvular tissue appeared in the atrial portion of the mitral cusp, causing obstruction to the mitral valve in an 18-day-old infant (That our patient was able to live to the age of 11 years was du to the subaortic ring which kept the pedunculated mass out of the actual valve aperture.) Since that time he has noted similar tissue attached to the ventricular aspect of the right atrioventricular valve which has caused subpulmonary stenosis. Both of these deformities were in patients with transposition of the great vessels.

It would seem unnecessary to discuss the lesion on the basis of an inflammatory etiology inasmuch as it had no such appearance on histologic examination. It has been pointed out that in cases of attempts at mitral reduplication the presence of other congenital anomalies is strongly suggestive that the lesion is a developmental anomaly [11] In this case ther was a bicuspid aortic valve an area of subaortic stenosis and a horseshoe kidney

It is our opinion that this lesion represents a *developmental attempt at duplication of* the anterior (aortic) cusp of the mitral valve.

Summary

An autopsy finding in a patient operated upon for subaortic stenosis was redundancy of the anterior cusp of the mitral valve. This consisted of a fenestrated sac-like structure on the inferior surface of the aortic leaflet of the mitral valve which communicated with *the left atrium* through three slit like apertures. This anatomic derangement is presented and compared to reduplication of the mitral valve in the reported cases.

It is believed that this represents a rare congenital anomaly not previously recorded in the literature.

A careful search of the literature reveals only three reports of similar lesions, briefly alluded to by Abbott Edwards [7] and Spencer and associates.[4] The present case, therefore, would be the fourth such anomaly reported

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Myocarditis in senescence

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Myocarditis is usually considered to be a disease of the younger age groups.[1-3] References reporting myocarditis in old age are rare. The few which we were able to find emphasize the cause and type of myocarditis rather than the diagnostic features differentiating myocarditis from coronary heart disease in the aged.

The purpose of this study is to stress the occurrence of myocarditis in old age in order to differentiate this from coronary artery disease and to see whether there is a special type of myocarditis more prevalent in this age group than in other age groups. A few pertinent references from the literature will be cited and a short summary presented of the clinical and pathologic findings in 10 patients between the ages of 60 and 69 years, and in 13 patients over 70 years of age. Several case histories and findings of unusual interest will be given in somewhat greater detail.

References to heart disease in the elderly patient are principally concerned with coronary artery disease and myocardial infarction. We are only aware of one study that attempts to differentiate between myocarditis and myocardial infarct.[4] However, there are a number of individual reports in which myocarditis has been mentioned as occurring in the old age group.[5]

Howell and Piggot[16] listed the main autopsy findings in 2,221 patients with cardiovascular lesions over the age of 65. Myocardial degeneration, including coronary disease, fatty infiltration, brown atrophy, atheromas, and calcification of the valves and vessels, was the most common cause of death. There was no mention of myocarditis. Rose and Wilson[6] attempted to find a specific cause of unexplained heart failure in the aged. They studied 50 consecutive autopsies on patients over the age of 70 who had clinically unexplained heart failure. Patients with valvular disease, severe coronary artery disease, hypertension, ventricular hypertrophy, anemia, pulmonary emphysema, malnutrition, thyrotoxicosis, or patients with cardiac failure as a terminal complication of pneumonia or of surgical procedures were excluded. These authors regarded three factors as a possible common cause of failure of the aged heart: (1) hypertension which had decreased due to failure, (2) myocardial ischemia, and (3) a degenerative process associated with aging, anatomic evidence of which was not described. They did not mention myocarditis. Scherf[7] describing cardiac arrhythmias in the aged, stated that there was no arrhythmia specific for old age.

Saphir and his associates[3] studied the

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hearts of 76 patients who had died from subacute bacterial endocarditis, 5 of whom were over the age of 60 Various anatomic changes in the myocardium usually focal including myocarditis, were present in all.

Zeman and Siegal discussed the cases of 9 patients with acute bacterial endocarditis over the age of 60 and Zeman[19] described the cases of 18 elderly patients with subacute bacterial endocarditis. Since acute myocarditis is a frequent complication of bacterial endocarditis, it would seem that some of these patients may also have had myocarditis. Wallach and his colleagues[21] found bacterial endocarditis with rheumatic heart disease in 82 of 509 autopsied patients 8 of these patients were over 60 years of age (9 7 per cent) Of 47 patients with bacterial endocarditis without rheumatic heart disease 10 were over 60 (21.3 per cent) In their comprehensive review of the literature they reported that 119 out of 1 472 patients (8 per cent) with bacterial endocarditis were over the age of 60 Hammond and Platts,[22] in a review of 1 000 autopsies of patients over the age of 60 found evidence of rheumatic disease of the mitral valve in 2.2 per cent.

In a study of myocarditis associated with bronchiectasis, Saphir[23] found myocarditis in 8 of 152 patients, 2 of whom were over the age of 60 The myocardial lesions were not characteristic The chronicity of the bronchiectatic lesion may have accounted for the subacute and chronic myocarditides. Clinically myocarditis could have been considered because of suggestive findings a 67 year-old patient had a heart rate of 128 per minute with a low-grade fever serial electrocardiograms were interpreted as showing an old myocardial infarction with chronic coronary insufficiency and with changing patterns of conduction Another patient 77 years old had diabetes and gangrene of a lower extremity On examination he had a rapid pulse with a temperature of only 100°F He died suddenly after amputation of the limb

Waller and co-workers[24] described the case of a 64-year-old woman who developed phlebitis and bacteremia. This was associated with severe weakness with episodes of irregular fever Autopsy disclosed a thymoma and severe myocarditis which resembled Fiedler's isolated variety and would have been so classified had not a similar type of myositis been found A somewhat similar instance of thymoma and granulomatous myocarditis with myositis was reported by Langston and his associates[25] in a 74-year-old woman The myocarditis was not recognized clinically in either of these 2 patients.

Hypersensitivity has played a role in a number of reported cases of myocarditis. Blanchard and Mortens[26] studied the case histories of 3 patients—68 73 and 85 years of age—who received sulfamethoxypyridazine (Kynex) because of infections of the urinary tract. In each case, autopsy disclosed an acute interstitial myocarditis with a marked exudation of eosinophils similar to other drug induced hypersensitivities. Again the myocarditis seems to have been clinically silent

Hodge and Lawrence[27] presented the cases of 2 patients who had hypersensitivity myocarditis after treatment with phenylbutazone One of the patients, a 70-year-old woman treated for osteoarthritis developed erythema multiforme and died unexpectedly in status asthmaticus. In the myocardium were multiple focal perivascular granulomas, composed of macrophages, inflammatory cells, eosinophils, and giant cells. Waugh[3] reported the case of a 60-year-old white man who had subacute pneumonia and was treated with penicillin He developed peripheral edema and died unexpectedly 7 days later At autopsy there was a diffuse interstitial myocarditis as well as focal granulomatous lesions in the liver kidneys, and spleen.

Rheumatic heart disease and its consequences, including myocardial complications, have been recorded in the elderly However acute rheumatic myocarditis and acute rheumatic fever are rare in senescence. Rogers and Robbins[28] described the cases of 41 patients, 7 over 60 years of age, in whom active rheumatic myocarditis was proved at autopsy although clinically it had been undiagnosed

Results

At Michael Reese Hospital we encountered 262 cases of myocarditis among 4 782 consecutive autopsies performed between 1950 and 1959 inclusive. Table I gives the age distribution of the patients

Table I Age distribution of myocarditis among 262 patients and incidence in each age group

Age group	Number of autopsies	Patients with myocarditis	Per cent of myocarditis
Newborn to 7 days	1 151	5	0.4
Infants through 1 year	383	15	3.9
Children 1-15 years	266	29	10.9
Adults 16-59 years	1 353	190	14.0
60-69 years	704	10	1.4
70 and over	925	13	1.4

Table II Severity of myocarditis in relation to coronary artery disease

Severity of myocarditis	Number of patients	Coronary artery disease		Healed infarct or fibrosis
		Severe	Slight	
+	3	0	3	0
++	3	1	2	1
+++	3	0	3	0
++++	14	7	7	7
Total	23	8	15	8

with myocarditis and the percentage of its occurrence in each age group. Myocarditis was present in 23 out of 1 629 patients who were 60 years of age and older, an incidence of 1.4 per cent. There were 10 patients between 60 and 69 years of age and 13 patients over the age of 70. Twenty-one of the patients were Caucasian; there were 13 females and 10 males.

Seventeen patients had a history of cardiovascular disease preceding their terminal admission. Twelve patients had arteriosclerotic heart disease with old myocardial infarctions, as diagnosed electrocardiographically. Three of these 12 patients had diabetes mellitus. Several patients had chronic angina pectoris. Others had congestive failure controlled by medication. Three patients had hypertension of many years duration. Two patients had rheumatoid arthritis. There were 2 other patients with a history of rheumatic heart disease.

Sixteen patients showed discrepancy between temperature and pulse rate. In many cases this was a sudden change associated with other cardiovascular findings—the sudden appearance of gallop rhythm, changing murmurs or murmurs in locations where not heard before, ectopic rhythms, or sudden onset of congestive failure. In most instances the clinical impression was acute myocardial infarction. On close review almost all patients showed evidence of *sudden change in cardiac status*.

Electrocardiograms were recorded at varying times during their hospitalization and often shortly before death. A change in contour attributed to arrhythmia or conduction defect was noted in 17 patients. There was chiefly atrial fibrillation and/or

Table III Etiology of myocarditis in patients over 60 years of age

Etiology of myocarditis	Number of patients
Secondary to diffuse bronchopneumonia	6
In instances of pyemia	3
Associated with acute endocarditis	1
Hypersensitivity*	6
Unknown (Fiedler)	7

*Includes toxic substances (norepinephrine).

A-V block or dissociation. Acute coronary insufficiency was believed to be present in 4 patients, and the possibility of a recent infarct with chronic coronary insufficiency was considered in 4 others. Chronic coronary insufficiency in the presence of right bundle branch block was reported once. None of these latter 9 autopsies disclosed recent myocardial infarction but there was marked atherosclerosis of the coronary arteries in 6 of these 9 instances.

Twelve patients died unexpectedly. Eight other patients went rapidly downhill or were in shock up to 24 hours before death. Three patients had a more gradual downhill progression for several days.

Autopsy findings

In 21 of the 23 instances the heart was enlarged. In 1 of the other 2 the patient was emaciated as a result of steatorrhea which might explain the small size of the heart. Thirteen patients showed foci of old endocarditis of the rheumatic variety—thickening of mitral leaflets or aortic cusps with some thickening of the chordae tendineae of the mitral valve. In one instance an acute bacterial endocarditis of the mitral valve was superimposed upon an old valvulitis.

Grossly in 17 patients the heart was flabby and/or dilated. There was severe coronary atherosclerosis in 8 patients. Three of these patients had an old occlusion of a coronary artery with resulting healed myocardial infarction. The hearts of the other 5 of these 8 patients showed various degrees of myocardial fibrosis. The other 15 patients had only slight coronary atherosclerosis, with wide patency of the arteries throughout. In no case was there an acute myocardial infarction.

Table II compares the severity of myocarditis with the degree of coronary artery disease in order to evaluate the role of myocarditis as a cause of death. Because of the relatively slight degree of coronary arteriosclerosis in some instances in view of the severity of the myocarditis, it would seem obvious that in at least 7 patients the myocarditis was the sole cause of death. The myocarditis in these cases was graded 4+ associated with only slight coronary arteriosclerosis. Moreover, in 3 other instances the myocarditis was graded 3+ and there was only a slight degree of coronary arteriosclerosis. It would seem that death in these additional 3 patients was also caused solely by myocarditis. Whereas in 7 other cases the myocarditis was classified as grade 4+, there was associated severe coronary arteriosclerosis. We believe that in these instances the myocarditis played a contributory role in the cause of death of these patients. In 6 other patients the myocarditis was graded either 1+ or 2+. Even though only one of these showed severe coronary arteriosclerosis, we believe that the myocarditis in all 6 instances should be considered coincidental. It should be re-emphasized that fresh myocardial infarction was not present in any one of the cases. Admittedly, coronary insufficiency was not taken into consideration since there is no definite way to prove its presence or absence from morphologic studies. From the foregoing it seems clear that myocarditis played a causative or contributory role in the mechanism of death in at least 17 of our patients.

The possible causes of the myocarditis in these 23 elderly patients are summarized in Table III. There were 10 patients with myocarditis after bacterial infections. Of these, 6 had diffuse bronchopneumonia and 4 pyemia. One of the patients with pyemia also had an associated acute bacterial endocarditis. Six patients had hypersensitivity myocarditis, and in 7 cases there was no associated disease to explain the presence of myocarditis so that these were classified as isolated or Fiedler's myocarditis.

In the hearts with myocarditis associated with pyemia, the myocarditis was usually diffuse and interstitial with numerous polymorphonuclear leukocytes and small abscesses in the interstitial tissue replacing small muscle fibers. In the cases which followed bronchopneumonia the infiltration was usually perivascular and interstitial and was predominantly composed of lymphocytes, Anitschkow cells, and a few polymorphonuclear leukocytes; serous fluid separated the muscle fibers. Young connective tissue could be seen in some areas around the blood vessels.

Thirteen patients had either myocarditis alone or changes in other organs presumably produced by the same agent that caused the myocarditis. The myocarditis

in most of these 13 instances was principally interstitial The infiltrate consisted prin cipally of lymphocytes and Anitschkow cells and a smaller number of polymorpho-nuclear leukocytes, plasma cells, histio-cytes, and rare fibroblasts. In a few in stances there were also large numbers of eosinophils Granuloma formations and giant cells were present in 2 cases, but Aschoff bodies were not encountered Some of the hearts showed collagen tissue both young and old in the interstitial areas, interrupting and occasionally replacing muscle fibers. Rarely was there isolated necrosis of muscle fibers. Edema was also present in varying degrees but was not so severe as in the cases of pyemia

There were 8 cases of old myocardial infarction or fibrosis which microscopically showed only broad bands of fibrous tissue in the myocardium interspersed with large thin walled capillaries and a few histiocytes with old blood pigment in their cytoplasm In no case could these changes be confused with m ocarditis

Histolog cally acute myocarditis and ery recent myocardial infarction may be d fficult to differentiate In both instances there may be large areas of polymorpho-nuclear leukocytic infiltrations However in recent infarcts the muscle fibers em bedded within the polymorphonuclear leukocytic infiltrate may appear to be densel eosinophilic show loss of their striations or be actually necrotic These changes involve all fibers within the in farct In acute m ocarditis however a polymorphonuclear leukocytic infiltrate is often interstitially located and if degenera tion or necrosis of muscle fibers occurs, either onl isolated muscle fibers are in volved or groups of muscle fibers. Instances of acute suppurative myocarditis may of course be easily recognized by the presence of abscesses.

In 6 patients the cause of the myocarditis was of special interest Because of its rarity these cases may be described in a little more detail. The degree and extent of myocarditis was graded 3+ to 4+ in all 6 instances. Four of these myocarditides were obviously hyperergic in nature. Three were the result of hypersensitivity brought about by drug therapy another one was that of an outspoken granulomatous myo-carditis associated with myositis. The granulomas were similar to hyperergic granulomas. There were acute polyarteritic changes in other structures. Two other instances of myocarditis were due to a toxic substance norepinephrine, associated with a pheochromocytoma and extensive therapy with Levophed respectively

Gross examination of the hearts of these 6 patients presented no unusual findings. In 3 the coronary arteries were patent in 2 there was some narrowing of the coro-naries with focal fibrosis of the myo-cardium and in 1 there was an old occlu sion of the right coronary artery with an old myocardial infarction in addition to the myocarditis. Three of these 6 patients died unexpectedly

Case reports

Case 1 A 71-year-old white woman was hos-pitalized because of pain in the right hip the diag nosis was trochanteritis and arteriosclerotic heart disease. At the time of admission she had a temper-ature of 100°F and a pulse of 104 per minute. She was given steroids and Aureomycin, 250 Gm. four times daily for 1 week. Diarrhea ensued and anti-biotics were discontinued. Several day later the temperature rose to 103°F the pulse t 160 per minute. An electrocardiogram showed first-degree A V block nd digitalis effect. She went nto shock nd died suddenly

At topsy the heart weighed 290 grams, was dilated and the right entricle showed severe fatty infiltration. The coronary ostia nd arteries were widely patent. The myocardium was somewhat softer than normal but showed no gross bnor malities.

Microscopic examination of the myocardium revealed diffuse interstitial and perivascular in-filtration composed primarily of Anitschkow cells and lymphocytes, few eosinophils, and rare mast cells. Often these cells formed conglomer tions imulating small gran lomas ithout gia t cells. A slight degree of fibrinoid degeneration was present between and around these granulomas (Fig 1). There was no necrosis of muscle fiber The small intestines disclosed few foci of acute periarteritis. The essel walls were edematous but ithout ne-crosis.

Case 2. A 77 year-old hite man with arterio-sclerotic heart disease tered the hospital bec use of suspected carcinoma of the prostate. The heart was enlarged nd there as a systolic murmur near the mitral area. An electrocardiogram showed chronic coronary insufficiency with suspected anteroseptal infarct, but no evolution was seen on serial electrocardiograms. H had been on long term Ga trin therapy after a cystotomy 10 months prior to death. He died suddenly while eating lunch.

A topsy disclosed a necrotizing angiitis of the



Fig. 1. Case 1. Myocarditis due to hypersensitivity (Aureomycin) in 71 year-old patient. Small and large eosinophilic cells with fibrinoid necrosis. Hematoxylin and eosin preparation. ×450.

kidney and prostate and an acute and subacute myocarditis, particularly involving the perivascular and interstitial areas. Within the myocardium the infiltrate in some fields formed small granuloma-like nodules around the blood vessels as well as between some muscle fibers (Fig. 2). Many areas showed young connective tissue interrupting and replacing muscle fibers, and this tissue was also infiltrated with inflammatory cells. The infiltration was composed of Anitschkow cells, histiocytes, eosinophils, lymphocytes, and a few polymorphonuclear leukocytes and fibroblasts. Some interstitial edema was present between muscle fibers. Away from the regions of the inflammation there were also areas of fibrosis obviously resulting from coronary sclerosis.

Case 3. An 88-year-old white woman was hospitalized with a 2-week history of vomiting and weakness. She had mild diabetes of 3 years duration and was treated only with Orinase, 1 Gm. daily. She had had some chest pain, and for 6 months had had peripheral edema. There was a systolic thrill on the left side of the neck with a Grade 4 systolic murmur. Jugular engorgement was marked and the heart was enlarged. A Grade 3 systolic murmur was heard over the aortic area. Neither blood pressure nor pulse could be obtained because of calcified arteries. Scattered râles were present throughout both lung fields. The clinical impression was marked coronary artery disease with congestive heart failure and atrial fibrillation. An electrocardiogram revealed intermittent A-V dissociation due to the operation of an accelerated slightly uneven nodal pacemaker and also first-degree A-V block.

She went downhill rapidly, became semicomatose, and died within a few hours. While in the hospital her only medication were digitoxin and NPH insulin.

At autopsy there was a focal necrotizing angiitis of the kidneys, uterus and periadrenal vessels. The heart was enlarged, dilated, and weighed 500 grams. There was moderate fatty infiltration. The mitral valve showed slight thickening of the line of closure of the leaflets and a small calcified nodule; the cusps of the aortic valve were thickened with slight fusion at the commissures. The ostium of the right coronary artery was markedly stenosed and its lumen completely occluded for a distance of 2.5 cm. The left coronary artery and its branches were patent. The myocardium was soft and mottled yellow-red in the posterolateral wall of the left ventricle and numerous streaks of fibrosis were also present.

Microscopic examination revealed a diffuse interstitial and perivascular infiltration of eosinophils and mononuclear cells in the myocardium extending through and disrupting the myocardial fibers (Fig. 3). There was only slight degeneration of myocardial fibers. The most striking feature was the marked perivascular infiltrate with slight fibrinoid necrosis of the vessel wall (Fig. 4). An onion-skin layer was seen around some vessels. Scattered myofibrosis, the result of old coronary sclerosis, was abundant. Acute arteriolitis and periarteritis with fibrinoid necrosis, polymorphonuclear leukocytes, and eosinophilic leukocytes within walls of arterioles and perivascularly were common in a number of organs and tissues. Except for the lack



Fig. 2. Case 2. Myocarditis due to hypersensitivity (Gantrisin) in 77-year-old patient. Perivascular granuloma with eosinophils and mononuclear cells. Hematoxylin and eosin preparation, ×170.



Fig 3 Case 3 Myocarditis due to hypersensitivity (Orinase 88-year-old patie t Perivascular onion-ski layer w th peri ascular infiltration of round cells. Fibrinoid degener tion of the essel wall is still present H matoxylin and eosin prepa ration X1 0.

of true ng tis the m ocardium the inflamma tory reaction was ery similar to that in other organs

Case 4 A 65- ear-old white man wh had history of hronic cholecystitis nderwent cholecystectom La er he developed difficulty in swal lowing Cl nically he ppeared to ha myasthenia gra is, although w th Prostigmine there was no improveme t. He was hospitalized because of marked muscular eakness, w th blood pressure of 154/90 mm Hg pulse of 140 per minut and temperature of 99°F A lectrocardiogram howed trial fibrillation w th rapid entricular response, suggesting changes due to position or acute coronary nsufficiency H was treated ith Prostigmine Achromycin, and Terramycin, and underwent a tracheostomy Unexpectedly he became cyanotic went into shock, nd died.

At topsy there was holedocholithiasis with dilatation of the common bile duct, acute cholangitis nd disseminated myositis. No thymus tissue could be found. The heart weighed 450 grams. The coronary artery ostia were patent and the myocardium showed small foci of fibrosis.

Microscopically there was principally inter titial myocarditis with isolated necrosis of muscle fibers. The infiltrate consisted of Anitschkow cells, lymphocytes, a few polymorphonuclear leukocytes, fibroblasts, and giant cells (Fig 5). The latter were of the reactiv ariety and seemed t be composed of Anitschkow cells. I the skeletal muscle ere small i terstitial foci of nflammatory cells, mostly mononuclears of lymphocytes nd few polymorphonuclear leukocytes with focal necrosis and degeneration of m scle fibers. It is interesting that the microscopic picture of the heart and skeletal muscle were almost identical. Anitschkow cells, however were found only the heart.

Case 5 A 60-year-old white woman who was hospitalized because of severe pain in the joints and back had had rheumatoid arthritis for 25 years and had recei ed teroid therapy for more tha 9 years. The pulse rate was 120 per minute, respirations were 20 per min t and blood pressure was 120/95 mm Hg Gallop hythm developed with a Grade 2 3 precordial systolic murmur A equaled P Râles were udible and the heart ppeared t be enlarged An electrocardiogram showed digitalis effect and possible coronary insufficiency She as treated for congest failure and the impression was decompensated rheumatic heart disease. Several days later he went into shock and developed ectopic trial tachycardia. Because the hemoglobin had fallen from 15 to 10 Gm over hort period of time transfusion was started. One hour later she developed a tachycardia of 150 and an electrocardiogram showed 3.2 A V block. She died shortly afterward.

Autopsy revealed osteoarthritic degenerative changes in the joints and subluxation of both rota. There was a pheochromocytoma in the left supra-

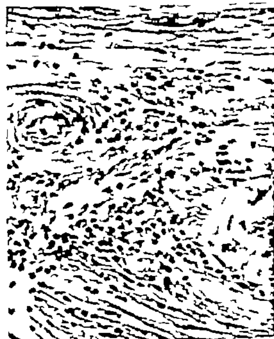


Fig 4 Case 3. Myocarditis due to hypersensitivity (Orinase) in 88-year-old patient. Perivascular infiltration of lymphocytes and polymorphonuclear leukocytes with fibrinoid necrosis of portion of essel wall. Hematoxylin and eosin preparation ×170.



Fig. 5. Case 4. Myocarditis due t hypersensitivity t in 65-year-old patien. Small gra loma w th giant cells. Hematoxyli nd eosi preparation. X295.

renal gland, measuring 2 cm in gre test diameter. The heart weighed 375 grams. The aortic al showed slight adherence between the cusps. The coronary arteries were paten throughou.

Microscopically the myocardial fibers were hypertrophied and the nuclei ere hyperchromatic. The fibers were separa ed by serous fluid in some areas and by loose connecti tissue in others. There were collections of inflammatory cells in the inter ti al issue, mainly l mphocytes, large monocytes, Anitschkow cells, fibroblasts fe pol morphonuclear leukocy es, nd mast cells (Fig. 6). There was abnormal amount of terstitial fibrosis. Isolated areas of severe degeneration of muscle fibers and even necrosis of small groups of fibers were found throughout.

Case 6. A 70-year-old Negro man was hospitalized for hemodialysis. H had history of h pertension and aortogram at another hospital had revealed an theromatous plaque in the left renal artery. An endarterectomy had been performed 2 weeks prior to admission t this hospital he aorta as clamped abov the renal artery for 40 min tes nd he went into shock for 30 min tes af er he oper tion. H was trea ed tha ime h an nknow amoun of Levophed. The blood pressure la er stabilized. After several day he became oliguric and then semicoma o e. The blood ure nitroge was 220 mg. per cen reatinine 14 mg. per ent CO₂ 15.5 mEq. l and potassium 5.6 mEq. L. V tal signs ere pulse of 120 per min te tem per ture of 103°F. nd blood pressure of 180/100 mm. Hg. A sof ystolic murmur over the pex, radiating to he precordium as heard. The im-pression was acute t bular necrosis and arteriosclerotic heart disease. An electrocardiog m showed sinus tachycardia and nonspecific electroly e hanges. After he was dialyzed, the blood urea nitrogen fell to 84 mg. per cent. Levophed was again gi en just prior to death. H remained semicomatose and died 3 day later.

At topsy there was marked generalized therosclerosis, acut tubular necrosis of the kidneys, and fibrinous pericarditis. The heart weighed 350 grams, was markedly dilated and there were patchy areas of subendocardial fibrosis. The mitral alv showed slight thickening of the leaflets and calcification of the cusps. The left coronary ostium was patent but the right was moderately stenotic. The coronary arteries were slightly narrowed by therosclerotic plaques bu patent throughout. The myocardium revealed scattered areas of fibrosis.

Microscopic examination showed an interstitial nd perivascular myocarditis w th lymphocytes, Anitschkow cells, histiocytes, some fibroblasts and polymorphonuclear leukocytes spreading part muscle fibers (Fig. 7). This infiltration was diffuse in some areas and was associated with focal necrosis of muscle fibers.

Discussion

E en though coronary artery disease and its complications are the most common type of cardiovascular disease in the elderly patient myocarditis does occur in a sig n ficant number. Among 1,629 consecutive



Fig. 6. Case 5. Myocarditis in 60-year-old patient w th pheochromocytoma. Severe degenerati changes in the myocardial muscle fiber with infiltration of lymphocytes and monocytes. Hematoxylin and eosin preparation, X295.



Fig. 7. Case 6. Myocarditis I. 70-year-old patient who had had mania. Levophed therapy. Severe degeneration of muscle fibers with infiltration by lymphocytes. Hematoxylin and eosin preparation. ×295.

autopsies of patients over the age of 60 there were 23 cases of myocarditis, an incidence of 1.4 per cent. Moreover among 925 patients over 70 years of age, myocarditis was found 13 times. Most of these patients had cardiovascular symptoms; many were in congestive failure. Others had a history of old myocardial infarctions and angina pectoris. However, in retrospect, all 23 of these patients at some time disclosed signs which could be interpreted as being caused by myocarditis[20]: murmurs that changed in intensity or location, gallop rhythm, sudden onset of atrial fibrillation or congestive failure, rapid pulse and heart rate with only slight elevation of temperature. The electrocardiograms recorded various changes in rhythm or conduction, but some were suggestive of acute myocardial infarction.

Knowing that myocarditis was present in these cases and analyzing in retrospect all the available data, we believe that certain observations should be stressed. Foremost is the knowledge that myocarditis does occur in senescence and that myocardial failure in every elderly patient is not necessarily due to coronary artery disease, old hypertension, valvular disease, or chronic pulmonary lesions. In every patient who develops evidence of impending myocardial failure, myocarditis should be taken into consideration as a differential diagnosis, notwithstanding the age of the patient. The realization that myocarditis occurs in the older age group will aid in the differential diagnosis. In our experience and on the basis of this study, the most important findings in diagnosing myocarditis are rapid pulse and heart rate with normal or only slight elevation of temperature. Fleeting changes in the electrocardiograms, gallop rhythms, etc., are of course important too. As stated, myocarditis was the main cause of death in 10 patients, and in 7 patients it was contributory.

Most interesting and unusual are the 4 patients with the hyperergic type of response whose cases we have presented above. The first 3 of these disclosed histologically a characteristic hyperergic type of inflammation. The myocardium was the seat of diffuse myocarditis with eosinophils, Anitschkow cells, and a few lymphocytes and polymorphonuclear leukocytes. There was also evidence of fibrinoid degeneration of perivascular areas. In addition, lesions in other organs and tissues were similarly characteristic of hypersensitivity changes. There was focal necrotizing angiitis with acute polyarteritis in organs other than the heart. Two patients gave a history of antibiotic therapy (Gantrisin and Aureomycin) and one had been treated with Orinase. Although Orinase had not been previously reported as producing this type of lesion, such lesions have been found to occur as a result of other antidiabetic drugs.[31,32]

The fourth patient presented a granulomatous type of myocarditis and also myositis, likewise presumed to have been drug induced. The nodular type of polymyositis which involves particularly perivascular spaces has been described to occur in association with collagen diseases,[33] but no evidence of such a disease was present. Polymyositis associated with myocarditis has also been reported in patients with myasthenia gravis[34,35] and was regarded as being similar to those which occur in hyperergic cases. Thus, although we are not certain as to the etiology of these lesions

in our case it seems most likely that they were also the result of hypersensitivity with granulomatous myocarditis and myositis due to a therapeutic agent which we have not been able to identify. The pathogenesis of such lesions has been reviewed by Angevine[34] in the discussion of the various causes of polyarteritis. He stated that vascular lesions in many conditions result from antigen antibody reactions. Although the basic mechanism may be similar different degrees of reactivity result in a wide variety of tissue alterations. Some of these may be acute and fulminating, with or without eosinophilia some may disclose an intense plasma cell reaction whereas others resemble granulomas with giant cells. The latter was present in our fourth patient. From this point of view all these myocardial alterations although of different specific etiologies, seem to have been produced by a similar mechanism.

Thus from the foregoing it is clear that hypersensitivity plays an important role in the causation of myocarditis in the elderly patient. It may be wise to question the indiscriminate use of antibiotics and other drugs, especially in an elderly patient. Perhaps if it is realized that this type of myocarditis occurs in the aged although less frequently than in a younger age group and that the elderly have perhaps more of a chance to develop hypersensitivity to various agents, the diagnosis will be made more often.

The microscopic pictures of the myocarditis of the last 2 cases were very similar. Both had obviously also the same etiology. L-norepinephrine, which is the basic secretion produced by pheochromocytoma as well as the synthetic variety (Levophed) have a similar effect on the myocardium.[37] The effect is primarily degenerative but is soon followed by inflammation with foci of acute necrosis of isolated muscle fibers. In time the inflammation is followed by repair and fibrosis appears, often separating and interrupting apparently healthy muscle fibers. This was seen in Case 3 in which there was both acute and chronic myocarditis. In the last case, the myocarditis microscopically corresponded to that seen in association with pheochromocytomas. As stated in the history an unknown large amount of Levophed had been given when the patient had postoperative shock and thereafter intermittently before his death. The changes were mostly acute but there were some early subacute changes which could date back to 2 weeks prior to his death.

Myocardial alterations with pheochromocytoma are common. Kline[33] found myocarditis in 4 of 7 patients with pheochromocytoma. Others have pointed out cardiac abnormalities in patients treated with large doses of Levophed.[39]

The myocarditis which was found in 7 patients in the absence of other significant disease may be classified as primary interstitial isolated or Fiedler's myocarditis.[40] This is a myocarditis of unknown etiology which is not associated with either endocarditis or pericarditis. The chronic forms of this type of myocarditis may simulate coronary artery disease or rheumatic heart disease.

The question is raised as to the importance of diagnosing myocarditis in senescence while coronary artery disease is so prevalent, and of differentiating between these two diseases in the light of a similar therapeutic approach. At the present time it is true that the differential diagnosis between these two diseases in persons of advanced age is merely academic, since we have no special therapy for myocarditis different from that used for coronary heart disease. However it has always been the prerogative of the pathologist to demonstrate a disease first anatomically and then to alert the clinician as to its presence. Thus, being aware of the coexistence of coronary artery disease and myocarditis, and of myocarditis in the absence of severe coronary arteriosclerosis in persons of advanced age, the clinician eventually will be able to differentiate between these conditions ante mortem. Later perhaps our armamentarium may include a more specific therapy for myocarditis.

Summary

Myocarditis is not rare in the aged. Among 1,629 consecutive autopsies of patients over the age of 60 there were 23 cases of myocarditis, an incidence of 1.4 per cent. Among 925 autopsies of patients 70 years and older myocarditis was found

13 times (1 4 per cent) Most patients had cardiovascular symptoms which were diagnosed as acute myocardial infarction All patients had characteristic clinical signs which in retrospect, could be interpreted as having been caused by myocarditis. Comparing the degree of coronary artery disease and resulting myocardial changes with the degree and extent of the myocarditides we believe that myocarditis was the main cause of death in 10 patients, and that it played a contributing role in the death of 7 patients. It was an incidental finding in 6 patients. Four myocarditides were typical of hypersensitivity and 2 were due to a toxic substance norepinephrine These cases were discussed in more detail Eight patients had evidence of old myocardial infarction or scattered fibrosis of the myocardium. In all hearts the anatomic changes due to coronary artery disease and infarction were distinct from the lesions of myocarditis. It was stressed that myocarditis is a specific entity of old age, as it is in younger individuals, that on critical evaluation of the patient the characteristic signs may be present, and that hypersensitivity plays an important role in the myocarditis of the aged.

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The hemodynamic significance of the radiologic changes in acquired aortic stenosis

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Chest roentgenograms are made routinely as part of the clinical evaluation of patients with aortic stenosis. The usual radiographic findings e g left ventricular enlargement aortic valvular calcification and changes in the ascending aorta are well recognized In order to make the chest roentgenograms in acquired aortic stenosis more meaningful the plain chest films of 50 patients with this disease were analyzed and the radiographic findings were correlated with the cardiac catheterization data

1 Selection of patients

The records of all patients with the diagnosis of valvular aortic stenosis in the experience of the National Heart Institute were reviewed From these cases were selected those which were considered to be of the acquired type by the following criteria (a) There was no history of a cardiac murmur during infancy or childhood (b) In the 30 cases in which the operation was done under direct vision there was no evidence of a congenital abnormality of the aortic valve. (c) In non operated cases there was a definite history of rheumatic fever or a clinical history which made a congenital lesion extremely unlikely (d) In the 15 patients who died pathologic study revealed acquired aortic stenosis.

Cases were then eliminated which showed a significant amount of aortic regurgitation as evidenced by an abnormally wide pulse pressure or by an aortic insufficiency indicator-dilution determination [*] beyond the level of the sixth thoracic vertebral body Also eliminated from the study were all cases which were complicated by involvement of a second valve an associated congenital defect or by frank heart failure.

2. Radiologic methods

The admission chest roentgenograms of the 50 patients with acquired aortic stenosis were analyzed for left atrial size left ventricular size and aortic dilatation In all cases, at least four views of the chest were available (posterior anterior lateral and both oblique views) Each parameter studied was graded without a knowledge of the hemodynamic data from 0 to 3+ indicating normal to markedly abnormal. In addition the presence of aortic valvular calcification was determined from the plain films and by fluoroscopy

The grading of the left atrial and left ventricular size and the aortic dilatation was done according to the following criteria

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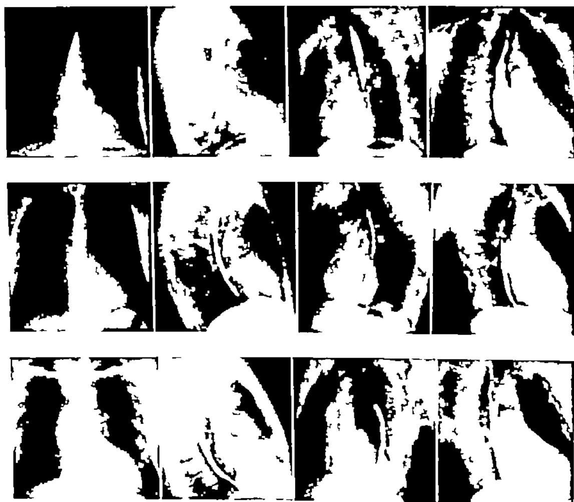


Fig. 1. Chest roentgenograms illustrating degrees of abnormality in acquired aortic stenosis. *Top*, Case 1—Left atrium +1, left ventricle +1, aortic dilatation +2. *Center*, Case 2—Left atrium 0, left ventricle +2, aortic dilatation +1. *Bottom*, Case 3—Left atrium 0, left ventricle +3, aortic dilatation +3.

A. Left atrial size. 0 — not enlarged. 1+ — slight enlargement as shown by (a) a slight localized deformity of the barium column on the lateral view in the left atrial region, and/or (b) a double density on the posterior-anterior view not extending to the right atrial border. 3+ — markedly enlarged as shown by (a) a large bulge on the lateral view which approaches the dorsal spine, and/or (b) a double density extending beyond the right atrial border on the posterior-anterior view, and/or (c) elevation of the left main stem bronchus. 2+ — moderately enlarged. Intermediate between 1+ and 3+.

B. Left ventricular size. 0 — not enlarged. 1+ — slight enlargement as shown by (a) an abnormal cardiac silhouette with globular rounding of the left heart border or a downward displacement of the apex, or enlargement of it just beyond the midclavicular line on the posterior-anterior view, and/or (b) a slight left ventricular bulge on the lateral view, and/or (c) slight encroachment on the vertebral bodies in the left anterior oblique view if done with approximately 60 degrees of rotation. 3+ — marked enlargement as shown by (a) a cardiac silhouette which approaches the left chest wall, and/or (b) a left ventricle which markedly overlaps the spine in the left anterior oblique projection if done with approximately 60 degrees of rotation, and/or (c) a left ventricle which

approaches the thoracic spine in lateral view 2+ — moderate enlargement intermediate between 1+ and 3+

C Aortic dilatation 0 — not enlarged 1+ — slight dilatation of the ascending aorta as shown by (a) a slight bulge of the aortic root to the right of the mediastinal shadow in the *posterior anterior* view and or (b) a slight bulge of the aortic root anteriorly in the lateral view and or (c) a slight bulge of the aortic root in the left anterior oblique projection 3+ — marked dilatation as shown by (a) a large bulge to the right in the posterior anterior view and or (b) an ascending aorta which approaches the sternum in the lateral view and or (c) a marked bulge of the aortic root in the left anterior oblique projection 2+ — intermediate between the foregoing criteria

Fig 1 shows the chest roentgenograms of 3 patients, to illustrate various degrees of abnormality

Catheterization techniques

All 50 *patients underwent catheterization* of the left side of the heart In 44 this was accomplished by the transseptal method [11,12] In the other 6 percutaneous puncture of the left ventricle[13] was performed Cardiac output was determined using the indicator dilution technique and the aortic valve area was then calculated by the Gorlin formula Quantification of aortic regurgitation by the dye-dilution *technique*[1] was performed in those patients in whom significant aortic insufficiency was suspected

Results

Analysis of the group of patients in the study showed that there were 39 males and 11 females. The average age of the males was 46 years and of the females, 47 years.

A Radiologic calcification of the aortic valve region in acquired stenosis For the purpose of analysis no attempt was made to separate calcifications of the aortic valves and *calcifications* of the *aortic* annuli, since in most cases the calcifications appeared to be a combination of these For descriptive purposes therefore all calcifications in the region of the aortic valves will be referred to as valvular calcifications.

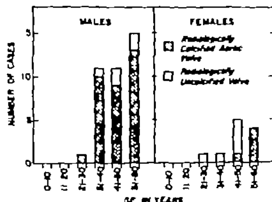


Fig 2. The distribution of radiologically calcified and uncalcified aortic valves, according to the age and sex of the patients, in acquired aortic stenosis.

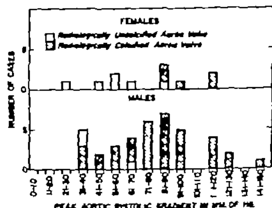


Fig 3 The distribution of patients with acquired aortic stenosis according to their peak aortic systolic gradients. Males and females are shown separately and radiologic calcification of the aortic valves is indicated.

The chest roentgenograms showed calcified aortic valves in 34 of the 39 males. No additional cases of calcified valves were detected fluoroscopically Of the 11 females, 4 were seen to have calcified aortic valves radiographically A calcified valve in 1 additional patient was detected fluoroscopically so that a total of 5 of the 11 females had calcified valves.

In Fig 2 the cases are distributed according to the ages of the patients, and the radiologic presence or absence of aortic valvular calcification is indicated It can be seen that for the males there is no special tendency for increased calcification with increased age The cases of calcification in the group of females tended to be among slightly older patients, but the num

ber of patients is too small to draw any definite conclusions. What does appear to be significant however is that whereas over 87 per cent of the males had calcified valves, this was the case in only 46 per cent of the females (p < 008) [14]

In Fig 3 the patients are distributed according to their peak aortic systolic gradients and the presence or absence of radiologically calcified aortic valves is indicated It should be noted that no radiologically uncalcified valves occurred in patients, male or female, who had gradients greater than 85 mm Hg Also all females with calcified valves had gradients greater than 80 mm. Hg

No direct correlation was seen between the presence of radiologic calcification of the aortic valves and the computed valve areas. Of those patients without aortic valvular calcification however only one had a valve area of less than 44 cm.

B Left atrial size in acquired aortic stenosis Analysis of the entire group revealed that of the 50 patients, 35 had radiologically normal left atria whereas 11 had slightly enlarged left atria and 4 had moderately enlarged left atria. No cases of markedly enlarged left atria were encountered

In Fig 4 the left atrial sizes have been plotted against the left atrial mean pressures. No left atrial mean pressures greater than 20 mm Hg were seen in patients with normally appearing left atria In fact, only 4 of 32 patients with normal left atria (13 per cent) had left atrial mean pressures greater than 12 mm Hg

Slight enlargement of the left atrium occurred with left atrial mean pressures of the same general range as for those without left atrial enlargement, except for a single patient who had a pressure of 41 mm Hg Elevated left atrial mean pressure, therefore cannot be predicted in acquired aortic stenosis from the presence of slight left atrial enlargement

Moderate left atrial enlargement however was not seen with left atrial mean pressures of less than 23 mm. Hg although only 3 cases fell into this classification.

In Fig 5 left atrial size is plotted against the left ventricular end-diastolic pressure. Inspection of this graph reveals that of the 15 patients with radiologically enlarged

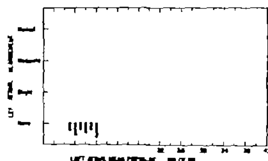


Fig 4 Left atrial mean pressure vs. the degree of left atrial enlargement in acquired aortic stenosis.

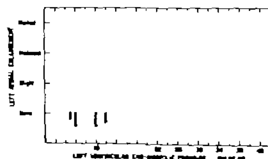


Fig 5 Left ventricular end-diastolic pressure vs. the degree of left atrial enlargement in acquired aortic stenosis

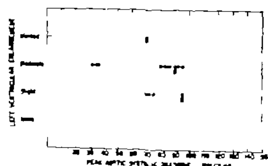


Fig 6 Peak aortic systolic gradient vs. the degree of left ventricular enlargement in acquired aortic stenosis.

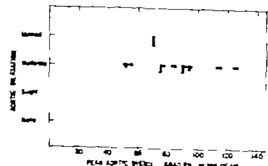


Fig 7 Peak aortic systolic gradient vs. the degree of aortic dilatation in acquired aortic stenosis.

left atria 11 had left ventricular end diastolic pressures greater than 15 mm Hg On the other hand only 3 patients with normal left atria had left ventricular end diastolic pressures greater than 15 mm Hg

Additional analysis of the data revealed no direct correlation between the presence of left atrial enlargement radiologically and the peak aortic systolic gradient or the aortic valvular orifice size

C Left ventricular size in acquired aortic stenosis Some degree of left ventricular enlargement occurred in 45 of the 50 patients in this series. Of the enlarged left ventricles, 16 were slightly enlarged 23 were moderately enlarged and 6 were considered to be markedly enlarged No direct correlation was present between the degree of ventricular enlargement and the age of the patients.

As is shown in Fig 6 no correlation existed between the left ventricular size radiologically and the peak aortic systolic gradient Additional analysis of the data revealed no correlation between left ventricular enlargement and aortic valvular orifice size peak left ventricular systolic pressure or the left ventricular end-diastolic pressure.

D Aortic dilatation in acquired aortic stenosis Radiologic evidence of aortic dilatation was the usual finding in this series of patients. Only 4 of the 50 patients had aortas which were classified as normal As is shown in Fig 7 however no correlation existed between the occurrence or degree of aortic dilatation and the peak aortic systolic gradient Similarly no correlation was present between aortic dilatation and the aortic valvular orifice size

Discussion

The method of selection of cases provided a group of patients with aortic valvular stenosis that was shown to be of the acquired variety by surgical or pathologic findings and or history No hemodynamically significant aortic regurgitation no second cardiovascular lesion and no clinical evidence of congestive failure was present in any of the patients. By all criteria possible, therefore this group represented pure aortic valvular stenosis of the acquired type and the preoperative radiologic findings seen should have reflected those changes due to the aortic valvular lesion

The method of radiologic evaluation is not so exact as would be desired since it is impossible from plain chest films to discern more than one border of any chamber Exact measurements are of greater value in determining over-all heart size when two borders can be seen in each view Even here, however there is inexactness since the size of the cardiac shadow varies considerably depending on the phase of the cardiac cycle in which the exposure is made. Also even slight degrees of rotation may significantly alter the size of the cardiovascular shadow particularly the silhouette of the aortic arch.[3] For these reasons, it was impossible to apply mensuration to determine the classification into which the left atria, left ventricles, and aortas belonged

As is necessarily the case when one is not using actual measurements, the classification of the structures being studied was quite subjective. As might be expected, there were borderline cases which might well have been classified into either of two groups. It was hoped that with only one observer (S D.R.) doing all of the classifying the discrepancies would be minimized It should be understood however that the classification used in this study resulted in a relative comparison rather than an absolute one. Nevertheless, the method used was practical in that in clinical radiology and in cardiology left ventricular and left atrial enlargement and aortic dilatation are not routinely determined by measurement, but are determined subjectively

Conclusions

A Conclusions in regard to aortic calcification in acquired aortic stenosis

1 The incidence of calcified aortic valves was much greater in males than in females (87 vs. 46 per cent) The average age of the male and female groups was the same, so that duration of disease probably does not account for the differences seen

2. All patients, male and female, who had radiologically uncalcified aortic valves, had peak aortic systolic gradients of 35 mm. Hg or less.

3 In a small group all females who had gradients greater than 80 mm Hg had radiologically calcified valves. In males, calcified valves were present with a wide range of aortic gradients.

4. There was no correlation between the presence of aortic valvular calcification and the aortic valvular orifice size. In this series, however absence of aortic valvular calcification generally meant a valve area of more than 44 cm.[2]

B Conclusions in regard to left atrial enlargement in acquired aortic stenosis

1 Some degree of radiologic left atrial enlargement was present in 30 per cent of the patients in this series. When it occurred it was usually slight in degree.

2 A radiologically normal-appearing left atrium was associated with a left atrial mean pressure of 20 mm Hg or less, whereas a slightly enlarged left atrium showed no direct correlation with the left atrial mean pressure. Moderately enlarged left atria were not seen with left atrial mean pressures of less than 23 mm Hg

3 In general left atrial enlargement was associated with a left ventricular end-diastolic pressure greater than 15 mm Hg

4. No correlation existed between left atrial enlargement and the peak aortic systolic gradient or the aortic valvular orifice size.

C Conclusions in regard to left ventricular size in acquired aortic stenosis

1 Ninety per cent of the patients showed some degree of radiologic enlargement of the left ventricle.

2 There was no correlation between the radiologic size of the left ventricle and the peak aortic systolic gradient the aortic valvular orifice size, the left ventricular systolic pressure, or the left ventricular end-diastolic pressure.

D Conclusions in regard to aortic dilatation in acquired aortic stenosis

1 A dilated ascending aorta was revealed radiologically in 92 per cent of the patients in this series.

2 There was no correlation between the occurrence or degree of aortic dilatation and the peak aortic systolic gradient or the aortic valvular orifice size.

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Subtle roentgenographic signs of left heart failure

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The majority of instances of congestive heart failure in the adult are due to disease which affects primarily the left heart, either the ventricle or auricle. Such diseases as coronary arterial disease, hypertension, or aortic valvular disease affect early the left ventricle, whereas mitral stenosis affects primarily the left auricle. Wherever the left heart fails, there is inadequate systolic emptying, the residual volume and end-diastolic pressure of the affected chamber increases, and subsequently the pulmonary venous pressure becomes elevated over its maximal normal mean value of 10 mm. Hg. In general, when the hydrostatic pressure exceeds 25 to 35 mm. Hg, the oncotic pressure of plasma proteins, fluid leaks through the pulmonary capillaries into the interstitial tissue. Increased turgidity of tissue occurs, with loss of compliance. The patient may experience dyspnea on exertion, paroxysmal nocturnal dyspnea, cough, and wheezing. Unless exudation occurs into the alveoli there may be no râles. Thus, the early hemodynamic change of left heart failure is pulmonary venous hypertension, and as Wood emphasized, there are no physical signs of pulmonary venous hypertension per se. The ultimate consequences of pulmonary venous hypertension are (1) interstitial pulmonary edema and (2) alveolar edema. Interstitial edema is much more common than the more advanced alveolar edema.

Many physicians think of left heart failure in terms of pulmonary congestion with râles. It is not widely appreciated that there may be no physical signs of left heart failure in the phase of interstitial edema, and, as Grainger[1] has emphasized, left heart failure can often be recognized radiographically before it is apparent clinically. It may be present in the absence of detectable cardiac enlargement, as in acute myocardial infarction or mitral stenosis. It may be present in the absence of tachycardia, ventricular diastolic gallop rhythm, pulmonary râles, peripheral venous dilatation, hepatomegaly, or edema (Figs. 3 and 8).

In order to suspect heart failure one must have a basis for heart disease. It may be diagnosed from the presence of conventional signs and symptoms. Less typical and nonspecific symptoms, such as insomnia due to Cheyne-Stokes respiration, easy fatigability, weakness, simulated hyperventilation syndrome, cough, unexplained gain in weight, nocturia, dizziness, somnolence, confusion, or palpitation due to extrasystoles, may at times be the predominant or initial clues. In infants increased respiratory rate and rapid pulse

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Table I. Data in 114 cases diagnosed as pulmonary edema by x-ray examination

Inadequate information for study					9
Clinical and x-ray diagnosis of pulmonary edema					71
Final clinical diagnosis					
Arteriosclerotic heart disease			46		
Acute myocardial infarction		6			
Hypertensive heart disease		3			
Thyrotoxicosis		1			
Rheumatic heart disease			15		
Hypertensive heart disease			2		
Renal disease			3		
Diffuse muscle disease			2		
Postpartum myocarditis		1			
Amyloidosis		1			
Congenital aortic stenosis			1		
Dissecting aneurysm			1		
Terminal cor pulmonale			1		
X-ray diagnosis of pulmonary edema—Missed clinically					27
Initial clinical diagnosis of cardiac or renal disease				10	
Arteriosclerotic heart disease			8		
Acute myocardial infarction		3			
Heart block		1			
Renal disease			2		
Neither cardiac or renal disease diagnosed initially				17	
Initial diagnosis					
Respiratory infection	10				
Acute abdomen	1				
Leg edema from pelvic tumor	1				
Bladder tumor	1				
Peripheral vascular disease	1				
Cerebral vascular accident	2				
Pneumothorax	1				
Final diagnoses in 17 cases					
Arteriosclerotic heart disease			14		
Acute myocardial infarction		5			
Hypertensive heart disease		1			
Rheumatic heart disease			2		
Diffuse muscle disease			1		
X-ray diagnosis of pulmonary edema subsequently unsubstantiated					7
Final diagnosis					
Viral pneumonia			3		
Carcinoma lung with lymphangitic metastases			1		
Leukemia			1		
Pulmonary fibrosis			2		

may be the early evidence of incipient heart failure.

While engaged in studies of the pulmonary veins with tomography, we became increasingly aware that one was often able to diagnose early left heart failure before it was appreciated clinically. Our statistics are not meticulous enough to give an accurate appraisal of the percentage of cases in which this was possible; however, in order to illustrate the approximate frequency, we have reviewed the cases which were cross-indexed as pulmonary edema in the radiographic files. All of these cases, with the exception of 8, were seen between 1959 and 1961.

A total of 114 cases was reviewed. Nine were excluded because of inadequate information. In 71 cases the clinical and radiographic diagnosis of pulmonary edema was in agreement. In 27 cases the diagnosis of pulmonary edema was suggested

*This study was supported by the Georgia Heart Association.

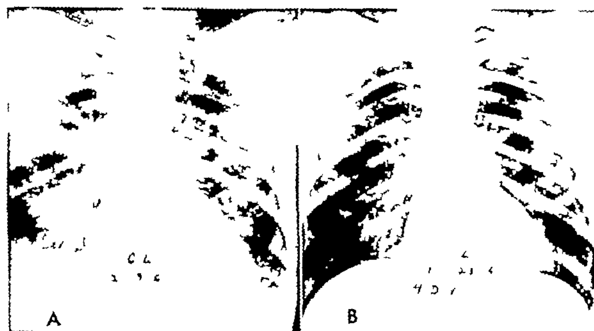


Fig. 4. C. F. ge 57 arteriosclerotic heart disease with old myocardial infarctions. Transient paroxysmal noct rnal dyspne de loped the night prior to the initial film (*A*). There were no râles, no cough no wheezing no entricular diastolic gallop, no enous distention no hepatomegaly nd no edema The pulse rate was 80. Not he clearing of he interstitial edema and collections of subpleural fluid in the costophrenic sulci in *B* 4 days af er digitalization nd diuresis.



Fig. 5. T. S., 41 mitral stenosis. Misdiagnosis of bronchiectasis in tially bec use of hemoptysis. N te dis tention of the superior pulmonary eins and costophrenic septal lines.

segmental lower lobe arterial branches.[18] In the normal radiograph of the chest the venous shadows tend to be rather inconspicuous, but with increasing pulmonary venous pressure these structures become more prominent. Early in the process of left heart failure the upper and lower lobe pulmonary venous tributaries are dilated to an equal degree. Left heart failure of more prolonged duration, as in mitral stenosis or chronic left ventricular failure, results in slightly different changes in the pulmonary veins.[18, 19] Vasoconstriction occurs in the lower lobe arteries and veins, with redistribution of a greater flow of blood to the upper lobes which in turn causes further dilatation of the upper lobe veins (Fig. 5). Laminography is very helpful in demonstrating the pulmonary vessels and facilitates the separation of the pulmonary arterial from the pulmonary venous structures (Fig. 2).

Because of frequent variations in the segmental venous drainage pattern of the lungs, no reliable measurements have been established for determining the normal range in size of individual segmental veins. However, with experience, as pointed out by Ormond and associates, one may become adept at recognizing dilated pulmonary veins. Recently, Lavenda and associates studied the relative dilatation of the upper and lower lobe veins in left ventricular failure and mitral stenosis on tomography and pulmonary angiography, and they observed that the most reliable measurements were obtained by finding the sum of the diameters of the apical vein of the right upper lobe at the level of the right upper lobe bronchus and the posterior segmental vein of the right upper lobe at the point at which it was crossed by the anterior segmental artery. The sum of the diameters of these upper lobe veins averaged 16.3 mm. in their normal subjects. Likewise, the sum of the diameters of the superior and inferior basal veins of the right lower lobe measured

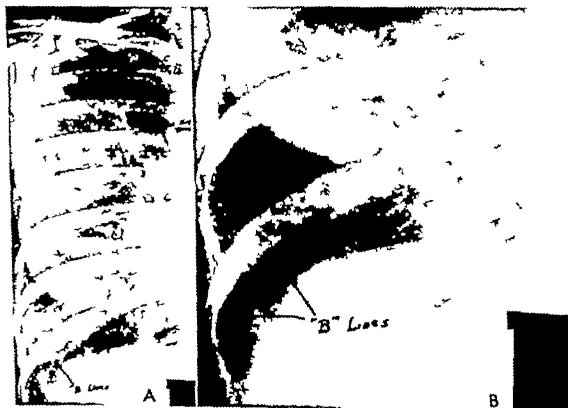


Fig. 4. L. O., age 43, mitral stenosis. This film demonstrates costophrenic septal lines, dilated superior pulmonary veins, and increased interstitial density (clouding) of the lungs.

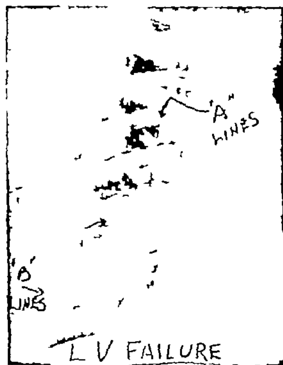


Fig 7 H P age 57 acute myocardial infarction. This film illustrates A and B septal lines, pulmonary loading and hilar engorgement.

1 cm from their junction averaged 18.1 mm In their cases of mitral stenosis the upper lobe veins averaged 19.4 mm., and in two groups with left ventricular failure these upper lobe veins averaged 17.4 mm. in one group and 21.2 mm. in the other

Interstitial pulmonary edema That the secondary lobule of the lung is the basic structure and functioning unit is now well established These secondary lobules are separated from each other by fine fibrous tissue septa which contain lymphatic vessels, and the pulmonary vein draining the lobule. Peripherally these interlobular septa lie perpendicular to the pleural surface and continuous with the subpleural fibrous tissue In the normal chest radiograph these fibrous tissue septa do not project a shadow since they are microscopic in size. In the event that these septa become markedly thickened by edema fluid fibrosis, or tumor cells, they become visible radiographically Kerley in 1933[6] first described fine, dense horizontal lines in the basal lung fields in patients with mitral stenosis and in 1951 he suggested that these might be due to dilated intercommunicating lymphatics or possibly to a type of pulmonary edema and arbitrarily called them B-lines (Fig 6) Similar lines more centrally placed nearer the hilum of the lung were referred to as A lines (Fig 7) Subsequent studies which have been excellently summarized by Grainger[4] have shown conclusively that these lines described by Kerley and also Fleischner[7] are in fact due to thickening of the fibrous tissue septa of the lung and, hence are best referred to as septal lines. Septal lines may result from any process which thickens or infiltrates the fibrous tissue septa. The most common cause is interstitial pulmonary edema of left heart failure. These septal lines have not been found unless the pulmonary capillary pressure is 18 mm. Hg or more and the pulmonary arterial diastolic pressure is greater than 25 mm Hg[4]

Radiographically septal lines appear as dense, sharply defined short lines perpendicular to the pleural surfaces, most often in the basilar portion of the lung They are horizontal in the lateral aspect of the lung but may be vertical when continuous with the diaphragmatic pleura (Fig 6) When due to edema these lines will disappear as the patient's circulation improves. In the central lung zones the interstitial septal planes are seen as straight or curved lines of greater length (up to several centimeters) and extend obliquely in any direction (Fig 7)

Fibrous tissue richly endowed with lymphatics surround all arterial and venous structures of the lung When edema fluid accumulates in the perivascular tissues, the involved vessel becomes hazy and indistinct in outline. This vague indistinctness of the larger pulmonary arteries and veins is a frequent sign of early interstitial pulmonary edema. The central lung zones become slightly increased in density as minimal fluid accumulates in the interstitial tissues, giving the lung a vague clouded appearance (Figs. 1 and 4)

The accumulation of fluid in the subpleural fibrous tissue planes of the interlobar fissures will produce a thickening of these fissures so that they become visible radiographically (Fig. 11) The accumulation of subpleural fluid in the costophrenic sulci may be quite prominent and

simulates free pleural fluid by producing obliteration of the sulci and thickening of the lateral pleural shadow

Pulmonary artery dilatation Closely following elevation of pulmonary venous pressure in left heart failure a passive elevation of pulmonary arterial pressure occurs. This is manifested radiographically as dilatation of the central right and left pulmonary arterial shadows. The right



Fig 8 W D age 53 acute myocardial infarction. The patient was admitted with abdominal pain which was misdiagnosed as an acute abdomen. The changes of interstitial edema noted in the lung bases in film *A* which was an upright abdominal film, led to the correct diagnosis. Film *B* shows further progression of the changes of interstitial pulmonary edema 2 days later



Fig 9 R. R., age 76, arteriosclerotic heart disease with old myocardial infarctions and pulmonary emphysema. Note in film *A* the changes of interstitial pulmonary edema and pseudo-tumor due to loculated interlobar pleural effusion. Considerable clearing in *B* 4 days after treatment for congestive heart failure.

I se lic k pul uo r rt rs I h I rm th r r asul r tru tur the r I t h lu I tl sr I tl Ir I I bee w ll st I lished n se ral tu I es N r n ll the maximum tran v rse liameter in a a lult varies betw en 9 and 15 mm.[4] In I ft heart failure wl en the ri ht de sce ding branch of the pulmonary artery



Fig 1 I S (I rosclerot he t d se se w th old m ardial d n ml as insufficiency Film I sh es I dia lema d lobular pe wh h may be mis k f pneumonia pul mary in f pulmona oplasm N t the le ng in B I w kal tine I I ges I later

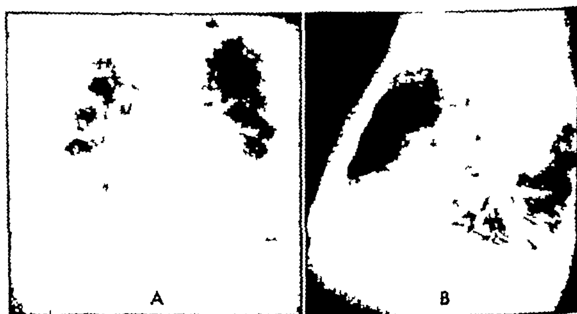


Fig 11 T. G., age 74 arteriosclerotic heart dise se with old myo rdial inf rctions Film I show type I changes of I terst tial pulmonary edema In the lateral film (B), fluid is seen i the posterior costophrenic sulcus, which cannot be ppreciated in the posterior teror iew There is lso thickening of the interlobar fissures, which is more asily pparent in the later l iew

is greater than 17 mm pressure in the pulmonary artery is distinctly elevated Perihilar clouding due to interstitial edema may obscure accurate measurement of the right descending pulmonary artery branch. This is especially true in acute left heart failure of sudden onset.

Pleural effusion. With further progression of left heart failure, transudation of fluid into the pleural space may occur (Fig 9) This may be a reflection of elevated systemic venous pressure but is also influenced by the pulmonary lymphatic drainage which may be impaired in the presence of pulmonary venous hypertension and interstitial edema. Minimal pleural fluid is manifested by obliteration of the sharpness of the costophrenic sulci Frequently this finding is evident only on the lateral view of the chest (Fig 11) Also minimal free pleural fluid obviously can only be demonstrated on an upright or decubitus radiograph Pleural fluid when unilateral is more frequently observed on the right side. Unilateral pleural fluid on the left side should alert one to consider an associated pulmonary infarction, since unilateral left pleural fluid is not commonly due to heart failure alone.

Intra-alveolar edema Intra alveolar edema is manifested radiographically by the presence of areas of increased density of varying size. The more easily recognized pattern is that of bilateral central confluent densities which have a "butterfly wing distribution. This pattern is produced by the accumulation of fluid within the alveoli with obliteration of their normal air content, and is seen in the more acute forms of left heart failure or renal failure. More limited forms of alveolar edema may present radiographically as a segmental consolidation indistinguishable from pneumonia pulmonary infarction or neoplasm The primary distinguishing feature is rapid change in appearance over a short period of time (Fig 10)

Cardiac enlargement Although in left heart failure the heart is usually increased in size there are frequent exceptions. In only 72 of our 114 cases was the cardiac thoracic ratio 50 per cent or greater Nearly all of the exceptions were in cases of either acute renal failure mitral stenosis (Fig 5) or acute myocardial infarction (Fig 8)

Summary

One hundred fourteen unselected cases in which the radiographic diagnosis was that of pulmonary edema have been reviewed. In 27 cases (24 per cent) the diagnosis of pulmonary edema was suggested radiographically at a time when this diagnosis was unsuspected clinically The radiographic changes in early left heart failure have been described in detail. These include dilated pulmonary veins increased interstitial density (clouding) of the lungs, septal lines, thickened interlobar fissures, and dilatation of the pulmonary artery and its major branches. More advanced changes include pleural effusion and alveolar edema.

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Acute nonspecific pericarditis complicated by the development of constrictive pericarditis

Two case reports

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There ... the ... ularly held ... that ... tive pericarditis ... ver ... a sequel of nonspecific pericarditis.

On the other hand, studies of patients with constrictive pericarditis ... al a large perce... cases of unknown etiology. This has suggested the possibility that some of these cases may have followed acute ... pericarditis.

It is the purpose of this paper to present 2 cases of acute nonspecific pericarditis that were complicated by the development of constrictive pericarditis within a relatively short time with subsequent pericardiectomy.

Case reports

Case 1. A 41-year-old salesman was first admitted to the hospital on Aug. 12, 1959, with the chief complaint of "hurting all over." He had been well until 1 week prior to admission when he ... with his wife and child had had ... virus infection. His symptoms were generalized malaise, myalgias, headaches, anorexia, diarrhea, and fever. The diarrhea subsided after 2 days, but the fever, malaise, myalgias, anorexia, and headaches continued. One ... prior to admission the patient had an increased fever, epigastric discomfort, slight dyspnea on exertion, dry paroxysmal cough, and chest pain with coughing.

There was a previous hospital admission in 1938 with ... -day history of upper respiratory illness. A chest ... film revealed ... the left base (Fig. 1 ...). The ECG was normal (Fig. 2 ...). He was treated symptomatically and recovered without sequelae in a few days. He remained well and ... symptoms during the interim. Other past history revealed "typhoid fever" when he was a child. There was no history of rheumatic fever or tuberculosis.

PHYSICAL EXAMINATION. Temperature was 100°F., pulse was 100 (regular). Respirations were 20 (not labored). Blood pressure was 100/75 mm. Hg with 10 mm. Hg pulsus ... He was a well-developed, well-nourished man in moderate distress. Examination of eyes and ears was normal. The pharynx was moderately injected with minute clear vesicular lesions on the ... pillars. The neck veins were not distended. The lungs were clear. Examination of the heart revealed sinus tachycardia, slightly ... sed sounds, ... greater than ... with the ... in ... but no ... cardiomegaly, murmurs, gallops, or rubs. The liver was percussed 3 to 4 fingerbreadths below the right costal margin, was ... tender to palpation and had ... muscle guarding. There was no edema. The neurological examination was normal.

CHEST X-RAY EXAMINATION. The cardiac silhouette was at the upper limit of normal size with some pleural effusion on the left (Fig. 1 *B*).

ECG. There was flattening of the T waves in Leads I ... and inversion of T in Leads II, III ... The QRS voltage was decreased as compared with the 1958 ECG (Fig. 2, *B*).

LABORATORY. The white blood cell count was 7,000 with a normal differential. Hemoglobin, 13.0. Urinalysis and VDRL were negative. Transaminase

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was 47 units. Sedimentation rate, 87 mm. per hour (Westergren). BSP 28 per cent retention in 45 minutes. Cephalin flocculation, negative. Thymol turbidity 1 Total bilirubin 0.6 mg. Serum cholesterol, 257 Antistreptolysin O titer 100 Todd units. C-reactive protein, 1 4 and 1 2. Heterophil agglutination, 1:14 Cold agglutination, negative. Agglutination series negative except for paratyphoid B titer of 1:80 and typhoid O titer of 1:40. First strength PPD negative. Five blood cultures negative. Lupus erythematosus preparations, negative. Serum electrophoresis showed decreased albumin elevated alpha 1 and alpha 2 globulins. Venous pressure was 145 mm. H_2O.

HOSPITAL COURSE. The patient was treated with bed rest, sedation analgesics, antiemetics, and antipertensives. On the day of admission, he had an episode of nausea, vomiting and shaking chill. On the third hospital day pericardial friction rub developed associated with increased dyspnea and chest pain (substernal without radiation and worse when he coughed or lay flat). He was placed in an oxygen tent for 2 days. A chest x-ray film showed slightly enlarged globular heart with pleural effusion in the left costophrenic angle. The right lung field was clear. The white blood cell count was 9,300 with normal differential. The hematocrit was 33.5 the hemoglobin, 11.8. Urine was positive for bile and had urobilinogen, 1:128. The urinalysis was otherwise negative. The ECG showed progressive S-T and T wave changes, with the S-T and T vectors almost parallel and 180 degrees from the mean QRS vector.

By the sixth hospital day the chest pain, cough, dyspnea, fever and friction rub were gone, and the patient was asymptomatic. However he continued to have râles in the left lung base (with x-ray findings of few linear plate-like areas of atelectasis with slight effusion) (Fig. 1 C), sinus tachycardia, and slight distention of the neck veins from the sixth to the thirteenth days. On the nineteenth hospital day he was discharged asymptomatic. The ECG continued to show T-wave inversion. A chest x-ray film showed the heart to continue to be slightly enlarged but with no evidence of the left pleural effusion, and the lung fields were clear. Urinalysis was negative. The white blood cell count was 5,150 with normal differential hematocrit, 42 hemoglobin 14 Sedimentation rate 35 BSP 28 per cent retention.

He was discharged on sedation. His discharge diagnoses were systemic viral infection pericarditis and/or myocarditis hepatitis ( ) He was rehospitalized 6 weeks later with history of having convalesced at home for 3 weeks. Then he began to work half day each day before he noted the return of dry cough (worse when supine), fatigue, aching, numbness of both arms, and tightness in the chest. Two weeks prior to this admission he had been digitalized for persistent tachycardia and an S_3 gallop.

PHYSICAL EXAMINATION. Temperature, 99.4°F pulse 104 (regular). Respirations 16. Blood pressure 100/80 mm Hg with 5 to 10 mm. Hg paradox. On this admission, HEENT was negative. He had marked distention of neck veins at 45 degrees, with increased AVC pulsation and positive hepatojugular reflux. The lungs were clear. The heart was not clinically enlarged and no apical impulse was felt. The heart sounds were slightly decreased. P was greater than A and was split on inspiration. A ventricular gallop rhythm was heard but there were no murmurs or rubs. The liver was palpated and percussed 2 to 3 fingerbreadths below the right costal margin and was tender. There was no edema.

CHEST X RAY EXAMINATION. The heart was within normal limits, and the lung fields were clear.

ECG. The electrocardiogram is shown in Fig. 2,C.

ANGIOCARDIOGRAM. There was reflux of dye into the inferior vena cava and hepatic veins, with poor opacification of the pulmonary arteries and delayed emptying of the right heart (Fig. 1,D).

LABORATORY. The white blood cell count was 6,650 with normal differential. Hematocrit, 43.5 hemoglobin, 14.8 Urinalysis negative. BSP 30 per cent retention. Thymol turbidity 3 Bilirubin, 2.4 total. LE preparations were negative. Second strength PPD was slightly positive. Histoplasmin skin test, negative. Sedimentation rate 74. ASO titer 100 Todd units. Venous pressure, 150 mm. H_2O circulation time 38 seconds.

HOSPITAL COURSE. The patient was again placed on bed rest, symptomatic treatment, and maintenance digitalis without diuretics. He continued to have marked discomfort in the chest, distention of the neck veins, tachycardia and hepatomegaly. The diagnostic studies and physical findings suggested constrictive pericarditis. On the nineteenth day an exploratory thoracotomy disclosed whitish, thickened, constrictive pericardium with diminished cardiac pulsations. Pericardiectomy was performed and few spotty areas of epicardial involvement were also noted. The heart bulged through as the pericardium was removed, and pulsated freely after the removal. Pathologic slides revealed fibrous tissue with chronic inflammatory cells and few areas of hemorrhage. There was no morphologic suggestion of tuberculosis or neoplasm. Smear and culture of the tissue revealed no fungus bacteria, or acid-fast bacilli.

The postoperative course was marred by hypotension, which was controlled with Levophed and an incisional infection which improved but continued despite local physical and systemic antibiotic therapy. He was discharged 1 month postoperatively doing well but with slight drainage from the incisional area. The ECG showed T to be positive in Leads II III V V-V where it had previously been negative but continued negative in Leads I V L, V-V (Fig. 2,D).

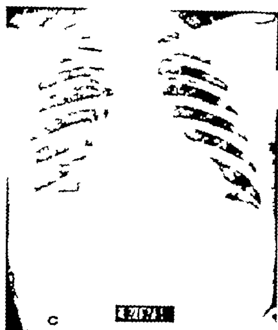
He had been taken off his digitalis on the twentieth postoperative day. He was discharged on vitamins, an oral analgesic, and sedation.

He did well and was asymptomatic after his discharge except for the persistent wound infection for which he was rehospitalized on Jan. 1 1960.

PHYSICAL EXAMINATION. Temperature 97.0°F pulse 88 (regular). Respirations, 16. Blood pressure 110/75 mm. Hg (no paradox). His general appearance was good. There was no distention of the neck veins. The lungs were clear. The heart was normal in size and sounds, with no murmurs gallops, or rubs. The liver was still palpable 2 fingerbreadths but was not tender.







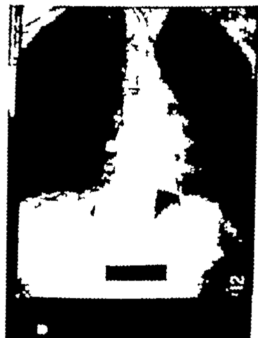


Fig 1 Case 1 A Film taken 1 y ar prior t h adm ssion t hospi l B 1 lm on dmissi showing pleur l ffusion on the left he rt large ha in previous film C Film 5 da la showing pla e-like mass f left side in addition t previous find g D V nogram 2 months la showing reflu f dy unt the inferior ena c and hepatic eins

SUBSEQUENT COURSE. The wire sutures from the pericardiectomy were removed the wound infection cleared, and he has since returned t work, nd present is ymptomatic

COMMENTS. After fairly typical pict re of cute nonspecific pericarditis, the patient developed constriction t bout 8 weeks and nderw t pericardiectomy t about 3 months. At the time of this writing 2 rs later he is doing w ll w bout a y know sequelae

Case 2 A 37 y ar-old man w first admitted to the hospital on Dec 19 1959 He had bee w ll

until 3) weeks prior to admission when be oke rth "band-like pressure across his mid-anterior chest associated with mild dy pnea. During the day be developed fever generalized malaise myalgias, nd dry hacking cough. H took self-prescribed erythromycl for 4 days, w thout improvement in y of the symptoms. He then took salicylates, other antipyretics, nd an amphetamine compound but all symptoms persisted essentially nchanged, ex cept for his cough, which became worse mainly at night, nd would follow tightness in his chest. One week prior to admission he developed some epigastric fullness and had one episode of dark urine. On the day before admission, physicia (seen in connection with the patient work) stated that he did not look well, and chest -ray film revealed marked cardiomegaly H was then re ferred to his pri ate physician and was hospitalized.

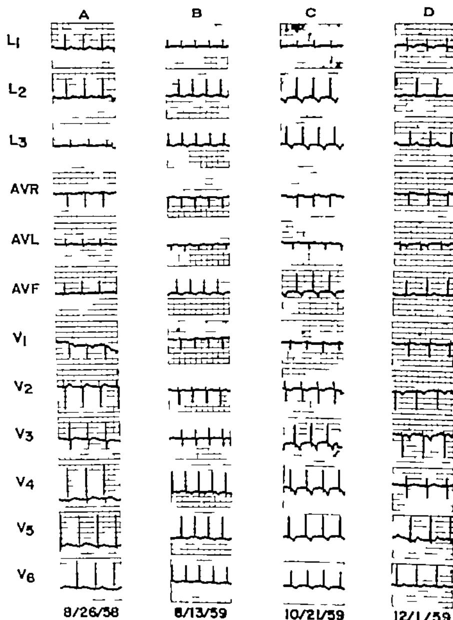


Fig C e 1 1 ECG taken 1 year prior to this admission t hospital *B* ECG taken the day of admission showing primarily T hanges. *C* ECG taken 2 months later prior pericardiectomy showing S-T nd T changes *D* Postpericardiectomy tracing wh h show improvement in the S-T and T es

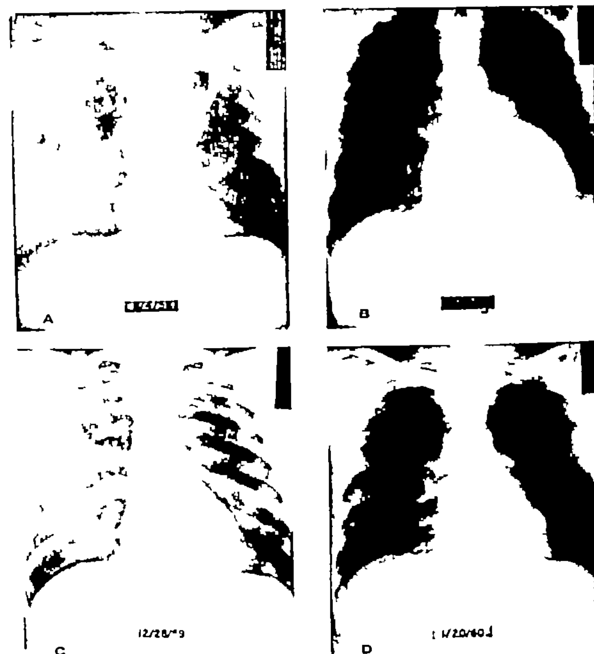


Fig 3. Case 2 1 Film taken over 1 y ar prior to this admission t hospital i normal. *B* I lm on admission showing marked ardiomegaly *C* F lm taken 9 day later show g decre se i heart size *D* Film taken hen patient had distention of the neck eins hepatomeg ly nd edema w th the heart even smaller than previously

In August, 1958, he had had mild t moder t episode of acut anterior pleuritic hest pain, followed in 24 hours by fever nd myalgia. A hest -ray film and ECG were normal (Figs. 3,A and 4 A). On ymptomatic treatment, the illness lasted 2 to 3 days, and he had been well since then. A complete examination Augu t 1959 was normal. The patient had worked in t berculosis sanitarium in the past, but there was no history of tuberculosis or heumatic fever

PH ICAL EXAMINATION. T mper ture 100°F pulse 100 (eg lar), respir tions, 24 (not labored). Blood pressure 110/80 mm. Hg with 20 mm Hg paradox. H as w ll-developed, ll-nourished ma in moder t distress and w th marked skin pallor HEENT examination as normal. The neck eins were distended t 45 degrees, w th positiv hepatojugular reflux. There was dullness in the left lung base with normal breath sounds. There were scattered heezes throughout both lung fields,

but no râles. Examination of the heart revealed the point of maximal impulse to be diffuse and ill defined. The left border of cardiac dullness was in the mid-clavicular line. A_2 equaled P_2. The heart sounds were distant. There was a Grade 2/4 short, blowing, decrescendo systolic murmur in the mitral area. A friction rub was heard best at the fifth intercostal space and was accentuated with inspiration. No gallop rhythm was heard. The liver was palpable 4 to 5 fingerbreadths below the right costal margin with a firm tender edge. There was a trace of pretibial edema. The remainder of the examination including the neurological, was normal.

CHEST X-RAY EXAMINATION. There was generalized cardiomegaly with a cardiothoracic ratio of 19.34. There was minimal pleural reaction in the left costo-

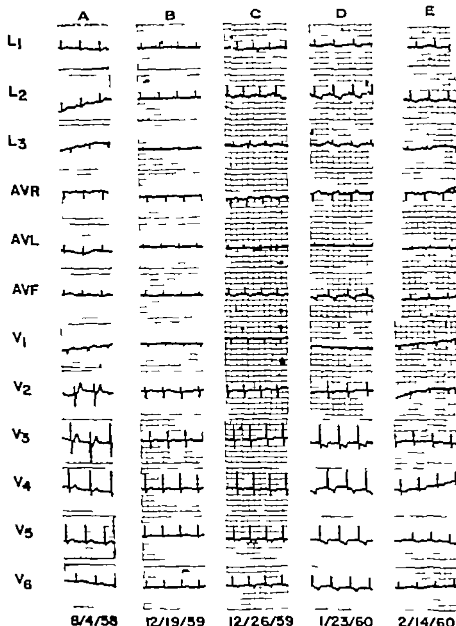


Fig. 4. Case 2. A, ECG taken over 1 year prior to this admission to hospital is normal. B, ECG taken on admission showing slight flattening of the T waves. C, Tracing taken 1 week later showing S-T and T changes. D, Tracing before discharge, first admission, showing progressive S-T and T changes. E, ECG prior to pericardiectomy showing some electrical improvement.

phrenic k There no ... of pulmonary edema (Fig. 3 B).

ECG QRS voltage w lo nd ther w light flatt ning of the T w es in the limb leads. There were no S-T han es ... (F 4 B).

LABORATORY The ... blood ... 12,000 ... normal ... 10.7 Hematocr t 31 ... and VDRL wer neg t ... Sedime t ... 32 mm per hour (West ... C ... pr tein ... ASO t ter 150 Todd ... BSP 29 per ... 45 min ... 3+ ... Five blood ... ce were ... venous pressur 105 mm H₂O. Circulation time 20 seconds.

HOSPITAL COURSE On the second hospital day pericardiocen s w s performed and 0 ... blood fluid w emov d hout d fficulty. Ex mination of the fl id rev led 6 5 wh t blood cells, mostly l mphoc es; hemoglobin w 1 5 Gm per ... nd the total protein 5.2 Gm per cent. Smear nd ulture rev led no fungi, bac teria, or acid-fast bac ll. C t log al xamin tion as neg ... for t mor ... After remo al of the fl id he had lessed pne ... chest film rev aled eduction ... heart size ... the postero- terior pr jection ... were not taken bec use of his se ... He w dig lized nd placed on trict bed rest, salt re st ictio nd ... He improved on this regi men nd ... the hospital ... he w ... nd had l 21 pound ... the neck ... were flat, the lu g ere lear the liver had decr sed t 1½ fingerbreadth ... nd the hemoglobin nd hematocrit had rise t 14.6 and 46.5 respectiv ly. His rdiac silhouett had decreased 15.5 – 31 m (Fig. 3 C). The ECG sho ed li ht S-T depression nd the T w es wer diph sic ... in Leads I, II, III, ... nd ... (Fig. 4 C). ... friction rub nd paradoxical pulse ontinued nd he had periodic ... odes of substernal pain which adiated t the ... lar area nd which w orse w th inspir tion ... of leaning forward. On the eighteenth hospital day be as begu on 60 mg of prednisolone day for 5 da w thout a ... significant hange. A hest ray film showed further decre se in ardiac size. The ECG sho ed progres sive S-T and T ha ges previousl ... leads. The neck eins ere flat, the lung ere lear nd the liver was not palpable. The heart ... was normal, w th no murmurs, gallops, or rubs. H as then placed on a regular diet nd gradual mbula tion. After 5 day on unrestricted salt he had gained 7 pounds, the neck eins had become distended, the liver had enlarged t 3 t 4 fingerbreadths, the lungs were lear nd the he rt examination as uncha ged. There was 10 mm Hg paradox. Chest fluoroscopy reve led lightly enla ged heart with markedly diminished pulsations (Fig. 3 D). The ECG was essentially unchanged (Fig. 4 D). Salt wa again restricted, nd diuresis produced 5- pound loss of weight in 3 days. H w sent home on bed rest and this regimen, but as then eadmitted t the hospital for surgery.

SECOND HOSPITAL ADMISSION H as rehos- pitalized on F b. 14, 1960 after 3 weeks t home on decreased act ity, salt restriction, diuretics, and digitalis, ha ing done fairly well ... the interim.

PHYSICAL EXAMINATION Temp r t 98.2 F, pulse 82 (... lar). Respir tions 18 (... labored). Blood pres r 105/60 mm Hg ... th 15 mm. Hg paradox. The neck ... d t ... at 45 de rees. The lun ere lear. The he t w ... lin ally ... A ... The heart sound re ... were no murmur , gallops or rubs. The li r palpable 3 fi ... breadth ... the right ... tal margin and ... pretibial edema.

ECG The ... showed ... (Fig. 4 E).

HOSPITAL COURSE On Feb. 15, 1960, ... direct my ... performed. The per ardi m ... thickened ... adhered ... hemorrhagic. There ... markedly diminished ardiac pulsations. The ... terior per ardium w ... with some dilata tion ... the heart w freed. Care was t ken t ... much of the ... tricting tissue around the area of the ... as possible ... thickened ... the ... markedly thickened ... There w re ... aggregates of hronic ... flammatory ... lls, ... small blood essel ... nd numerous foci of hemor rhage. Throu hout ll section ther ... were no tumor cells. Cultures were not made.

The patient had ... postoperative ... and w ... discharged on Feb. 27, 1960 ... constriction ... approxi mat ly 6½ weeks after the onset of ... and underwent peric rdiectomy t about 10½ weeks. At the time of th ... little ov 1 ... later he is doin w ll, worki g full time ... y known sequelae.

Discussion

There have been many follow-up series of acute nonspecific pericarditis in which no cases of chronic constrictive pericarditis have been found as sequelae. Levy and Patterson[?] in 1950 followed 23 of 7 patients with "acute sero-fibrinous peri- carditis" from 6 months to 16 years, with 17 patients followed for more than ? years. They found no cases of constrictive peri- carditis. Carmichael and associat s in 1951 reported a follow-up of 43 patients with acute nonspecific pericarditis. Twelve of these were followed for more than 9 years. They found no cases of constricti e pericarditis. Wood in 1961 states that "none of my cases originally classified as benign has subsequently constricted." Other follow-up series without develop- ment of constrictive pericarditis include those of Scherl[?] (96 cases), Govette[?] (78 cases), Chapman and Overholt[?] (?0 cases), and McCall and Hertz (18 cases).

Review of the literature revealed 4 previ- ously reported cases of constrictive pericar ditis following acute nonspecific pericard tis.

Freilich[18] in 1952 reported the case of a 52 year-old man who had constrictive pericarditis that was found by fluoroscopy and electrokymography 6 years after the first 3 or 4 episodes of acute nonspecific pericarditis.

In 1954 Krook reported a follow-up of 21 patients with acute nonspecific pericarditis. Two of these, a 40-year-old man and a 51 year-old man developed constrictive pericarditis 6 and 20 months after the initial episodes.

In 1954 Rabiner and associates[7] reported the case of a 40-year-old man who had constrictive pericarditis that occurred about 2½ months after acute benign pericarditis, massive pericardial effusion and repeated pericardiocenteses.

A possible fifth case is that of a 54-year old woman reported by Carmichael in 1951 she was found to have pericardial calcifications 4 years after an episode of presumably acute nonspecific pericarditis.

In 1961 Connolly and Burchell commented on 3 patients in whom chronic constrictive pericarditis developed 2½ months, 4 months, and 4 years after the occurrence of typical acute nonspecific pericarditis. A fourth patient developed constriction after suffering an initial acute pericarditis 4 years previously with recurrences 3 years and 1 year previously These were not reported cases, but were mentioned as part of a 10-year survey of pericarditis.

Of the 11 cases cited constriction occurred within 6 months of the initial episode in 6 cases and after 4 years in 4 cases. The earliest occurrence was in Case 2 6½ weeks the longest was 6 years (Freilich[18]) Two of the 4 patients in whom constriction occurred 4 years after the initial episode had 2 or more recurrences.

Since the 2 cases reported here occurred within 4 months of each other in a relatively small general hospital it makes one suspect that the disease may not be so rare as was previously believed.

Summary

The literature is reviewed and 2 cases of constrictive pericarditis after acute nonspecific pericarditis are presented Constriction occurred at approximately 8 and 6½ weeks, with pericardiectomy at 13 and 10½ weeks, respectively The question is raised whether the disease is as rare as was previously believed

I should like to express my thanks to Dr Edward Russell and Dr Spencer Brewer for allowing me the use of their cases in this report, to Dr Walter Bloom and Dr Carter Smith for their critical review and to Mrs. Margaret Eickhoff Miss Sue Pritchett, and Mrs. Betty Pause for their technical assistance in preparing this paper

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Experimental and laboratory reports

A clinical study of the first derivative of the brachial pulse. Normal standards and abnormalities encountered in heart disease

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Records of the brachial pulse derivative have been studied in this department for the past 3 years. Our original purpose was to use these records to throw light on the interpretation of force ballistocardiograms taken simultaneously[1] and for exact timing of the duration of rising pressure. However, as clinical experience grew we soon discovered that such records were of great interest in themselves. Since we have now secured these records in over 175 persons, it is possible to define preliminary normal standards and describe the abnormalities most commonly encountered in disease.

Records of the pulse derivative bear a relation to those of the conventional pulse which is identical with that between records of the distance traveled by your car and the speed as given by the milage meter and the speedometer, respectively. The modern developments in electrical engineering have made it easy to convert the conventional pulse, when secured by an electrical transducer, into a record of its first time derivative and so to record the speed at which the blood pressure rises and falls at every instant. Records of this type have been secured before,[2-4] and the first derivative of the ventricular pressure pulse has been studied in several patients.

Methods

Apparatus. A capacitance transducer made after the design of Brecht and Boucke[4] was used to sense the pulse. We modified it by the substitution of a short bar for the button used to make contact with the artery. The differentiating circuit used has already been described, as well as the tests to assure ourselves that it was adequate.[5] To obtain a record of the pulse derivative, two channels were needed, the first for the conventional pulse, the second for the derivative. A Sanborn Twin Viso was well adapted for this purpose. When simultaneous records of the pulse derivative and electrocardiogram or ballistocardiogram were desired, 3 channels were needed.

Subjects. The healthy subjects were medical students, doctors on the staff of the hospital, visiting doctors, and hospital employees. The great majority of the patients were drawn from the wards and outpatient department of the University Hospital. All were ambulatory.

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Tests The subjects had had no food for the 2 hours preceding the test. They lay comfortably in the horizontal position on an ultra low frequency or a high frequency ballistocardiograph The transducer was applied with the bar at right angles to the course of the brachial artery and bound on with a strap Several positions were tried and that giving the best, that is the most normal record was used. After a rest period of 15 minutes or longer the following records were taken in pairs pulse derivative and conventional pulse pulse derivative and electrocardiogram and finally pulse derivative and force ballistocardiogram Auscultatory blood pressure was taken several times after the end of the preliminary rest period

In each test the base line of the derivative record was determined by cutting down the gain of the amplifier *used for the record of the conventional pulse* until the derivative record became a straight line Similar treatment of the ampl fier *used for the reco d of the derivative* changes the centering of that record and could not be used to determ ne its base line

Calibration Simultaneous records of the derivative and conventional pulse and the auscultatory blood pressure permitted us to calibrate the derivative after the test the method used is exactly described in the legend of Fig 1 in which such records are pictured and in which the letters used to designate the main features of the pulse derivative are given Since the cal bration had to be made after the run there was no way of making the rec ords taken during our tests comparable in size. To compare ampl tudes of the pulse derivative records shown in our figures one must refer to the calibration given beside the reproduction of each record.

Clinical study Using the diagnoses of the ward chiefs, who had no knowledge of the results of our studies we classified the patients, according to criteria given in a previous communication into the clinical groups recorded in the tables.

Except n one nstance when we had more than one satisfactory test on any subject, only the results secured on the first have been used n this study The exception was a case of arteriovenous fistula tested before and after its closure.

Clinical data such as those obtained from history x ray studies, and electrocardiogram were taken from the hospital records, so that these data were secured by persons who had no knowledge of our results.

The ballistocardiograms cited were all described and recorded by the senior

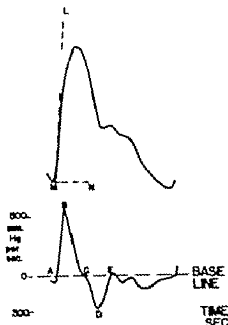
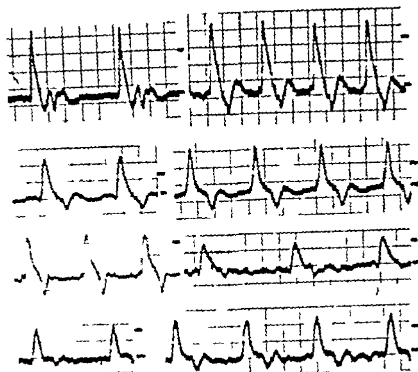


Fig 1 Conventional pulse record nd its first deri tive with respect to time Letters are used to identify the arious features of the deri tive Calibration of the ertical scale of the derivativ f om simultaneous records with the pulse is made as follows the point of maximal slope of rising pressur on the con entional pulse w f ont is located it is immediately above the main peak of the derivative taken simultaneously A line (ML) is dr wn tangent to the conventional pulse at this point. The ngle of this line ith the horizontal (LMN) is read ith protractor Its tangent is corrected for the dimensions obtaining when the record was taken, as follows If w find erage auscultatory blood pressure, 120/80 mm. Hg pulse pressure = 40 mm. Hg. Average pulse amplitude measured on the record = 20 mm. Speed of record 1 mm. = 0.04 sec. Angle LMN = 85° tan. 85° = 11 4 Then corrected maximal slope of con ventional pulse = 11 4 × 40/20 × 1/0.04 = 5 0 mm Hg/sec Distance of peak of deriv ti (B) above the base line = maximal slope of conventional pulse = 570 mm. Hg/sec. Base line of derivati e, found by experiment has value of 0. The calibration of the deri th is linear and the values of these two point giv alues to every position on the ertical coordinate, hich can be inserted as is show above Time values for the horizontal coordinate come directly from the record timer



F... Typical normal records of the brachial pulse deriv... secured in healthy persons and those without heart disease. Calibration is linear; base line and 300 mm Hg ... are shown to the right of each record. *First row, left*: M.S., age 25, B.P. 114/94 mm Hg, in good health. *First row, right*: S.S., age 42, B.P. 176/80 mm Hg, mild diabetes. *Second row, left*: F.L., age 52, B.P. 152/96 mm Hg, good health. *Second row, right*: A.S., age 46, B.P. 140/96 mm Hg, good health. *Third row, left*: H.R., age 52, B.P. 150/100 mm Hg, ... ECG ... *Third row, right*: T.W., age 55, B.P. 118/75 mm Hg, good health. *Fourth row, left*: B.B., age 29, B.P. 102/65 mm H..., good health. *Fourth row, right*: R.C., age 40, B.P. 123/...0 mm Hg, good health.

ad antages ... er th ballistocardiogram and so... disad anta... the ... hal of the latter will be discussed next.

All the well known technical difficulties inherent in getting a record of the pulse by a transducer placed on the skin o... r an artery affect th... deri at ve as well as the conventional record, a... d they constitute a serious problem. The substitution of a short bar for the conventional button placed at right angles to the course of the artery has improved our records considerably for artifacts caused by lateral movement of the vessel have been greatly diminished. But many problems remain, especially those concerned with the tightness of the binding of the transducer to the arm. If the binding is too loose, the high frequency information we seek is not recorded; if too tight, discomfort may be caused and the record becomes distorted because the artery is compressed too much and the blood pressure is applied to the transducer in directions to which it is not sensitive. In Fig. 5 we show the differences found in normal records of the same person when the tightness of the binding is varied. Obviously, the difference is considerable.

Because of the great difference between the muscularity of arms and the depth of arteries, we have not been able as yet to d... fine proper binding in terms of pressure applied. The best we can offer at this time is the suggestion that several positions and several pressures of binding be tried and that the choice be made on the appearance of the record secured. After one learns to a... oid bindings which are obviously too loose or too tight, one accepts the most normal-looking record he can obtain. But even with much experience

variations in the way the transducer is applied to the skin over the artery make some difference in the record.

Needless to say, we asked ourselves whether puncture of the artery was not the solution for all such difficulties, and with the help of Dr H W Linde and Dr S. Deutsch this was tried. We found that in some cases there was more high frequency information in the records secured by the transducer outside the artery than in records secured through the

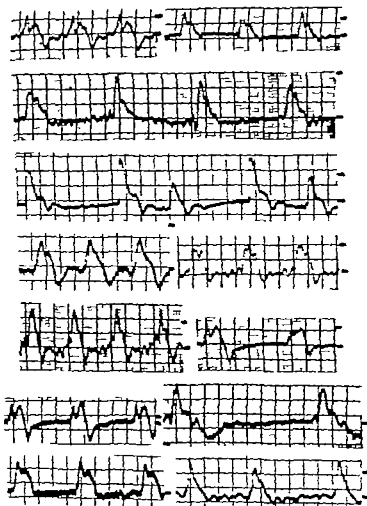


Fig 3 Typical abnormal records of the brachial pulse derivative secured in persons with cardiac disease. Calibration is linear base line and 500 mm. Hg/sec. are shown to the right of each record *First row left* M.J age 62, B.P 144/90 mm. Hg coronary heart disease *First row right* H.B., age 53, B.P 144/94 mm. Hg former cardiac infarct. *Second row* R.H age 63, B.P 136/78 mm. Hg, angina pectoris. *Third row* W J age 34, B P 112/60 mm. Hg, R H D mitral and aortic stenosis, auricular fibrillation. *Fourth row left* K H., age 53, B.P 120/80 mm. Hg, R.H.D., aortic stenosis. *Fourth row right* P S., age 55 B P 168/100 mm. Hg, R.H D aortic stenosis. *Fifth row left* J H age 55, B.P 200/130 mm. Hg, H C.V D *Fifth row right* M. McC., age 56, B P 124/72 mm. Hg, R.H.D mitral stenosis *Sixth row left* S.G age 78, B.P 122/58 mm. Hg hepatitis, L.B B.B. *Sixth row right* S G., age 67 B P 152/72 mm Hg former C H.F A-V conduction defect *Seventh row left* M G. age 59 B P 125/90 mm Hg, chronic pulmonary disease *Seventh row right* C N age 75 B P 166/78 mm. Hg angina pectoris.

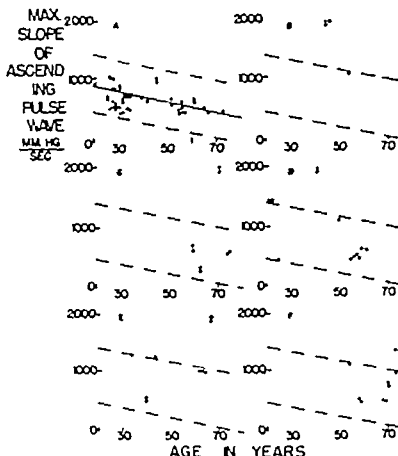


Fig. 4. The maximum slope of the ascending brachial pulse wave front (the height of the main upward peak of the derivative) plotted against the age of the subject. A, Healthy persons; the solid line is the regression of maximum slope on age; the broken lines are placed 2 standard deviations away on each side and define normal limits. The broken lines in the rest of the figure are similar to those of A, both defining normal limits for healthy persons; they permit one to recognize the normality or abnormality of the data secured on any patient. B, Results secured in hospital patients without evidence of heart disease. C, Results in the coronary group. D, Results in the rheumatic heart disease group. E, Results in the hypertensive heart disease group. F, Results in the miscellaneous heart disease group. Arrows attached to dots indicate that the value was off the scale in the direction indicated.

needle. Since our chief interest lay in such "high frequency" phenomena, we have explored the field with the simpler technique before seeking to improve the intra-arterial methods at our disposal to meet the stringent requirements of high frequency recording.

In healthy persons with normal pulse derivatives no variation in technique will produce records which resemble those found in many persons with abnormal hearts. Also in those with abnormal records no variation in the technique short of binding so loose that it is obviously inadequate will produce normal-appearing records. Therefore we have felt justified in going forward despite a considerable error but one obviously not great enough to account for the striking differences we find.

Since records of the pulse derivative are unfamiliar to most, it seems best to discuss their relation to more familiar aspects of cardiac function before discussing their unique contribution to our knowledge of cardiac performance.

Relations of the pulse derivative.

A. RELATION TO THE CONVENTIONAL PULSE. The amplitude of the derivative indicates the steepness, or the slope of the conven tional pulse at each instant. The peak of the chief upward wave of the derivative (*ABC*) is synchronous with the steepest point of the ascent of the conventional pulse, and the tip of the chief downward wave of the derivative (*D*) is synchronous with the steepest point of the descending pulse. Whenever any part of the conven tional pulse wave is horizontal the deriv ative is on its base line.

The derivative emphasizes certain aspects of the conventional pulse and suppresses others. Thus, high frequency phenomena such as angles notches, and slurs, so small that they are difficult to recognize on the conventional record be come very conspicuous in the derivative. In contrast, low frequency phenomena, such as the wandering of the base line with respiration so common an artifact in pulse records, are filtered out of the derivative, i.e. so reduced that they are hardly detectable. For this reason the derivative is somewhat easier to record than the conventional pulse its record does not wander about.

The *average* slope of the conventional pulse, the pulse pressure divided by the duration of rising pressure, previously studied in this laboratory bears no necessary mathematical relation to the *maximum* slope, measured by the height of the chief peak of the pulse derivative a major interest in this present study But in many cases the two vary together so that, in our data abnormalities of average slope are usually but not always, accompanied by corresponding abnormalities of maxi mum slope.

B RELATION TO THE ECG We have had several cases of bundle branch block in which there was a resemblance between the countour of a single lead of the ECG and that of the pulse derivative taken simultaneously needless to say the other ECG leads showed no resemblance to the

Table V Normal time values for the brachial pulse derivative duration of segments and waves measured on the base line (in sec /100) Data from 68 healthy persons

Age	Number	AB		BC		CD		AC	
		Mean		Mean		Mean		Mea	
20–29	17	4 8	0 73	9 1	1 7	13 6	1 7	13 9	1 9
30–39	19	4 6	0 51	9 7	1 9	13 5	1 9	14 3	2 1
40–49	11	5 2	1 1	11 3	3 1	9 8	1 9	16 4	3 6
50–59	15	5 7	1 6	12 8	2 8	10 1	3 1	18 5	3 2
60–73	6	6 0	0 58	15 0	2 3	7 8	1 5	21 0	2 5

Table VI Normal values for the brachial pulse derivative duration of segments and waves meas ured on the base line in per cent of the cardiac cycle. Data from 68 healthy persons

Age	Number	AB		BC		CD		AC	
		Mean		Mean		Mean		Mean	
20–29	17	5 9	1 1	11 3	2 7	16 2	3 8	17 3	3 4
30–39	19	3 3	1 0	10 9	2 4	15 3	3 1	16 2	2 7
40–49	11	7 1	1 2	15 1	4 0	13 3	2 7	22 1	4 4
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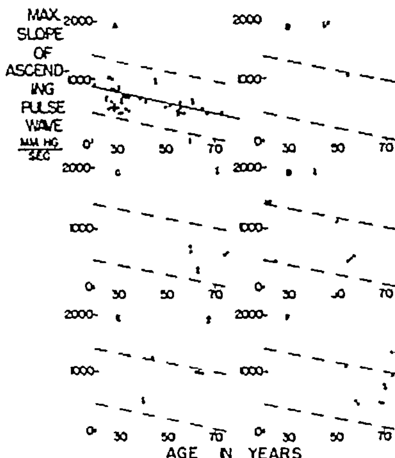


Fig. 4. The ma um m slope of the d scend g br hial pulse w front (the hei ht of the main upward peak of the deriv t e) plotted g in t the ge of the subject. 1. H althy pe son the solid line is the gr sion of ma imum lope of e the broken lines are placed 2 tanda d deviations y on ach side and define normal limit. The broke lines in the rest of the figure are simi la t those of 1 by defining normal limit for healthy persons, they permit one t recognize the normal ty or bnormality of the data secured on ny patient. *B* Result secured i hospital patient without evidenc of heart dise se. *C* Results in the oronary group. *D* Result in the rheumatic heart disease group. *E*, Results in the hypertensi heart dise se group. *F* Results in the misc llaneous heart dise se g oup. Arrow ttached t dot indic te that the lue was off the scale in the direct on ind ted.

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Table V Normal time values for the brachial pulse derivative duration of segments and waves measured on the base line (in sec./100) Data f om 68 healthy persons

Age	Number	AB		BC		CD		AC	
		Mea	σ	Mean	σ	Mean	σ	Mean	σ
20–29	17	4 8	0 73	9 1	1 7	13 6	1 7	13 9	1 9
30–39	19	4 6	0 51	9 7	1 9	13 5	1 9	14 3	2 1
40–49	11	5 2	1 1	11 3	3 1	9 8	1 9	16 4	3 6
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Table VI Normal values for the brachial pulse derivative duration of segments and waves measured on the base line in per cent of the cardiac cycle Data from 68 healthy persons

Age	Number	AB		BC		CD		AC	
		Mean		Mean		Mean		Mean	σ
20–29	17	5 9	1 1	11 3	2 7	16 2	3 8	17 3	3 4
30–39	19	5 3	1 0	10 9	2 4	15 3	2 1	16 2	2 7
40–49	11	7 1	1 2	15 1	4 0	13 3	2 7	23 1	4 4
50–59	15	6 3	2 3	15 3	3 4	11 9	3 6	22 1	4 3
60–75	6	6 7	1 3	16 5	2 5	7 2	4 1	23 2	3 3

pulse der ati e in these ses There has not bee ny resemblance betw en the nt ur the pulse derivati e and that f ny k f the ECG in ther cases M sn lern nh l to have had so ltt pern s il rec rds of me han l r ha p rt r si that they r t pr l r bel s that the usual re ularit of the ECG i licates a similar re ularity of the han l function of th h rt l l a s the lt n not true l l 6 sult n su cord h w how u h la t r heat s hanical irr ularit s ur les te n unchanged ECG l trast l 6 he how an alter nat n ECG u which u y us diffe n es th l trual recor l are not a com p r ll l t t lle differences in mechan l perf r nce

REL TI N T THE F R E BALLIST R RA WAVE Th r lat n is so interesting th t t has been tudied separately and th results ll be reported in another n nunic t on

Other considerations

Con ern ng o no mal group In our series of 68 health persons th re are dif ferences of sex and ra as has been de scribed Regression equation which re lated max mum elo it of the pulse ascent with a e were alculated for these groups separ tel Their slopes were so similar that we ha e used the regression of the group as a whole as the basis for our pre liminary ormal standards

Normal records of the pulse derivative Typical examples of norm l record are shown in Fig 2 At the arri al of the pulse there is a sharp take-off angle at *A* (Fig 1) occasionally preceded by a small very brief downward deflection The *AB* seg ment is smooth and rises sharply to a single peak at *B* The descending *BC* segment is not so steep as the preceeding ascent and is usually concave upward The principal downward peak at *D* is sharp The distance of *D* below the base line is about one third that of *B* abo e it After *D* there is usually a small upward peak that may or may not reach the base line at *E* followed by a descent after which the record gradually approaches the base line to reach it just before the arri al of the next pulse Between the wave tip at *D* and the commencement of the followi wave at *A* there may or may not be sm waves superimposed on the usual diastol patt rn Compar son of Fi with Fi h ws clearly that many of the mine differences between normal records can b attributed to differences in the ti htnes with which the transducer is bound t the arm

The most interestin sin le measureme made on the derivative is the amplitude o the main upward wave the vertical dis tance from its tip (Fi 1,*B*) to the base line The calibration gives thi measure ment a finite value which defines the maxi n um velocity of the rising pressure in mill meters of mercury per second. This value diminishes with the age of the sub jects even thou h good health continues (Fig 4) a finding which is obviously con i tent with the weakenin of the cardiac c ntraction as age advances

Measurements of the duration of the chief wave on the base l ne have an at tractive simplicity because no cal bration is needed They can be expressed directly in units of time or r latively in per cent of the ardiac cycle the latter a justs for differences in heart rate

In healthy persons the duration of the main upward deflection *AC* increases with age, since the weakening heart re quires a longer time to raise the pressure to its maximum

The diminution of the duration of *CD* with age is shown in Tables V and VI The finding i consistent with the following explanation During this period at the very end of ystole—the period between the pressure peak and the dicrotic notch of the con entional pulse—the pressure in the great vessels, although falling is still supported by the cardiac energy since ejection is not over In older persons, cardiac output is not so well sustained throughout systole so that the pressure at the end of systole falls off faster and its maximum rate of fall is attained earlier than in youth

Abnormal forms of the pulse derivative Most ab normal records can be identified by inspection alone as is evident from a comparison of Fig 2 with Fig 3

Among the *abnormalities of contour* not hes and divided waves are the most

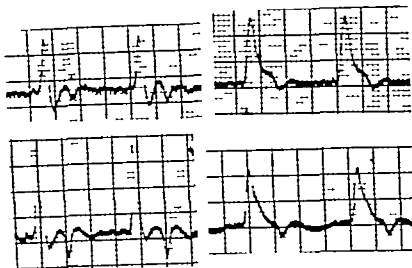


Fig. 5. Illustration of the effect of differences in the tightness with which the transducer is bound to the arm. *Upper row:* C.L., normal. At the left, the transducer is bound on very tightly; at the right, the binding is loosened. *Lower row:* D.N., normal. At the left, the binding is much too tight; at the right, the binding is loosened.

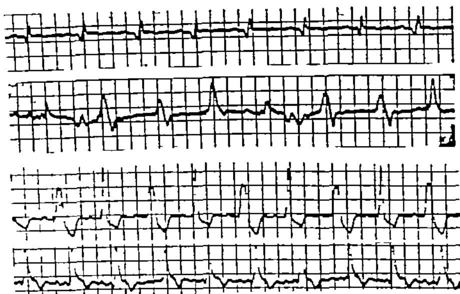


Fig. 6. Contrasting electrical and mechanical aspects of cardiac function. *Upper pair:* S.O., age 64, who has recovered from a cardiac infarct. Lead II of the ECG above the simultaneous record of the brachial pulse derivative. Note that the ECG is constant, whereas the pulse derivative indicates marked beat-to-beat variation in the mechanical performance of the heart. *Lower pair:* F.P., age 74, hyperthyroidism (?). Lead II of the ECG above the simultaneous record of the brachial pulse derivative. Note alternating ECG without any indication of corresponding change in the mechanical function of the heart.

conspicuous and they occur most frequently. These notches and divided waves represent angles, slurs, and tiny notches in the conventional pulse which might well escape attention. Such irregularities in the conventional pulse were readily reproduced in cadaver preparations by simulating a systole in which the ejection of blood was jerky. Therefore, when similar abnormalities of the pulse emphasized in the record of the pulse derivative occur during life, they are clearly to be interpreted as indicating that the cardiac contraction has lost its normal smoothness.[7]

One should expect, however, that the *peripheral pulse would not contain evidence* of this type of cardiac abnormality unless such abnormality is very much pronounced, for it has long been known that small notches present in the pulse in the aorta are damped out before the pulse reaches the periphery.

Table III shows that this type of abnormality was detected in the pulse derivative of 43 of our patients. In all of these the routine clinical study gave strong evidence of cardiac abnormality. However, such abnormal notches in the pulse derivative were also found in 4 persons who believed themselves to be healthy. In these our studies were limited to electrocardiograms and ballistocardiograms, and the latter were abnormal in all of these 4 persons. To date only one case has been encountered in which a pulse derivative that showed abnormal notches and divided waves was not accompanied by an abnormal ballistocardiogram. The relation between these two records is close and has been discussed elsewhere.[7]

Abnormalities of amplitude. Inspection of Fig. 4 and Table IV shows a result anticipated by the findings of a previous study.[6] Although many of our patients had severe cardiac abnormality as judged from conventional studies, not one of them gave a pulse derivative with an amplitude significantly *less* than normal for that age. *In a number of cases the* maximum velocity of rise in blood pressure was conspicuously *greater* than normal despite the fact that in these same patients the routine clinical studies often gave strong evidence of cardiac abnormality as is shown in Table IV.

Much the same finding, equally unexpected, appeared in our study of average pulse slope,[6] and our explanation of the recent results is similar to that given before. The slope of the conventional pulse and the amplitude of the pulse derivative are controlled by two factors. The first is obviously the strength of the heart's beat, but a second factor lies in the peripheral resistance, for when that resistance is high a larger fraction of the cardiac effort goes initially into the potential energy which creates the pulse than when the resistance is low.[8] The vasoconstriction which accompanies a weak*ening heart not only* maintains the blood pressure at normal levels but, by increasing the percentage of cardiac energy going into pressure, masks the weakness of the heart to one who is observing the pulse.

The patients judged to be abnormal by the standards for maximum velocity shown in Fig. 4 are largely the same group previously judged to be abnormal by the standard for the average pulse slope. Table IV gives the results of the clinical study of all those not previously described and the initials of the others so that their clinical data could be readily secured from Table II or from the previous paper[6] by anyone interested.

Abnormalities of wave duration. Abnormalities of wave duration of the pulse derivative seemed worthy of a quantitative study because of the simplicity of making *the measurements on any record equipped* with a timer. Also, since in healthy persons the duration of the chief upward deflection (AC) and of its descending segment (BC) increase as age advances, it seems evident that this measurement indicates a weakening of the heart as age advances. The older heart takes longer to raise the pressure to the point of maximum velocity, from A to B in Fig. 1, to the point of maximum pressure, from A to C, and to go from one to the other, from B to C. Since cardiac weakness due to age is detected by such *measurements,* it is reasonable to expect that the cardiac weakness due to disease would be readily detected also.

Defining the normal limits as within twice the standard deviation about the regression of the measurement and age, we find that when AC duration was mea-

ured in absolute time units, 7 of our cases were detected as having abnormally broad *ABC* waves in the pulse derivative. When the duration of this wave was measured in per cent of the cycle 11 cases were judged to be abnormal in all of which there was additional evidence of cardiac abnormality in the routine study

Measurement of the duration of *BC* in the derivative, the length of time between the point of maximum velocity of pressure rise and the peak of pressure of the con ventional pulse, proves to be somewhat more sensitive in detecting abnormality in our patients. By means of the absolute measurement 19 cases were detected as being abnormal by the relative measure ment 13 were detected in all of which there was strong evidence of cardiac disease in the routine study These results suggest that the weakening heart is unable to sustain the vigor of its contraction througbout systole and that studies made at the end of systole may detect myocardial weakness earlier than those made at the beginning

Relations between different types of myocardial abnormality In this study the hearts of many of our patients have been judged to be abnormal by both the old and the new methods. But a large number of our patients who were judged to have abnormal hearts by the clinicians in charge of their care gave perfectly normal pulse derivatives. Certainly this finding should occasion no surprise to those who see the trend of the newer cardiology Cardiac abnormality must be divided to understand it. One must first distinguish between the anatomic and physiologic abnormalities of the heart During the past medical generation under the influence of the great school of pathology conventional cardiac diagnostic methods have been aimed chiefly at detecting anatomic abnormalities, and most of the con ventional cardiac diagnoses have been and still are anatomic diagnoses. But the pulse, like the ballistocardiogram gives physiologic information relative to the ability of the heart muscle to meet the demands put upon it Thus, the heart of a man with an anatomic abnormality such as mitral stenosis, may be beating adequately or it may not. The heart of a man subject to attacks of a certain type of pain angina pectoris may be beating adequately or it may not. The aim of the physiologic methods is not to confirm or deny anatomic diagnosis but to give useful information about the way the heart is performing and to record the effect of treatment upon its performance.

The serious functional abnormalities of the heart must be further subdivided into the two aspects so conspicuous in abnormalities of peripheral muscle function weakness and incoordination These may or may not occur together The aspects of the pulse derivative which indicate incoordination—notches and divided waves in the contour—identify as abnormal a group of patients quite different from those identified as abnormal by the amplitude of the record which is related to cardiac strength and weakness, as is shown in Table VII And it also appears that a non cardiac physiologic mechanism peripheral vasoconstriction can influence the re lationship between the strength of the pulse and the strength of the heart making it unlikely that diminution of the magnitude of either the conventional pulse or its derivative will permit the diagnosis of the initial stages of cardiac weakness.

A glance at the abnormal records of the pulse derivative shown in Fig 3 and those pictured in previous communications shows that the chief evidence of cardiac abnormality given by these records lies in abnormalities of contour and form and these can be detected by inspection alone Many of the abnormal records are notched indicating incoordination of cardiac con traction Their upward deflections may be unduly broad indicating that the weakened myocardium requires more time to raise the pressure. The take-off angle may be rounded indicating lack of the usual snap at the onset of ejection. In our ambulatory patients the hearts which give such records have been successful in keeping the blood pressure within the normal range or above and the pulse has not become noticeably weak. But these hearts are struggling to keep the circulation going normally and the struggle shows plainly in the abnormalities of contour so obvious in many records of the pulse derivative.

Summary

Records of the first derivative of the brachial pulse have been secured in over 175 subjects, 68 of whom were healthy persons and the rest of whom were ambulatory hospital patients. Such records emphasize certain features of the conventional pulse such as angles, notches, and slurs, and suppress other features, such as the slow movements of the base line.

From data secured on the healthy subjects normal standards have been defined for contour, for amplitude of the chief deflection, and for the durations of the main waves on the base line. As age advances the main wave of the pulse derivative diminishes in amplitude and becomes broader on the base line, even though health is maintained with one's age is retarded.

Conspicuous abnormalities of the contour of the pulse derivative were identified by inspection in 43 hospital patients, in 11 of whom conventional hospital studies gave strong evidence of cardiac abnormality. Four persons who believed themselves to be healthy showed similar abnormalities of the pulse derivative contour.

The amplitude of the main wave of the pulse derivative indicates the maximum rate at which blood pressure rises on the advancing pulse wave front. Amplitudes greater than normal were found in 25 patients. No one was encountered who had an amplitude less than normal; the reason for this is discussed.

Abnormalities of wave duration were identified in a small number of patients—the exact number depended on whether this duration was expressed as time or as per cent of the cardiac cycle.

Changes in the amplitude and duration of the main wave of the pulse derivative permit one to identify aspects of the cardiac performance which change as age advances. These indicate the normal weakening of the myocardium as one grows older. Abnormalities of contour of the pulse derivative indicate an incoordination of the cardiac contraction.

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Electrical alternans with emphasis on recent observations made by means of single-cell electrical recording

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The purpose of this paper is to present a brief review of recent developments in clinical and experimental electrical alternans. Particular emphasis will be given to observations made by means of single-cell electrical recording.

History

The phenomenon of electrical alternans was first described in the experimental animal by Hering in 1908. The alternation which involved the ventricular complex was produced by means of glyoxylic acid administered parenterally. Subsequently its occurrence was reported by Lewis, in 1910, in man during a bout of paroxysmal atrial tachycardia. In 1936 Schutz[3] produced alternation of the form and amplitude of the monophasic injury potential (demarcation potential) in frog and rabbit hearts by warming the sinus region. In 1954 Hoffman and Suckling using the microelectrode technique, found alternation in the rate of repolarization of the transmembrane action potential in single fibers of dog papillary muscles driven at rapid heart rates. No variations in magnitude were observed. The authors did not mention any simultaneous recordings of the transmembrane action potential in the single fibers and the surface electrogram of the papillary muscle.

In 1956 Kleinfeld, Magin and Stein produced electrical alternans in single ventricular fibers of the intact frog heart by means of L-thyroxine, triiodothyronine, and acute hypoxia. The phenomenon was transitory, unrelated to heart rate, and more often than not associated with decreased cardiac contractility. Alternation of four types was observed: (a) in the rate of depolarization, (b) in the rate of repolarization, (c) in the magnitude of the action potential, and (d) in the magnitude of hyperpolarization. The alternation in the rate of depolarization and of repolarization of the transmembrane action potential correlated with the electrical alternans of the QRS complex and T wave, respectively. Recently, electrical alternans was pro-

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duced by us in single fibers of the sinoatrial node atrioventricular node bundle of His and ventricular fibers of the rabbit heart and in single fibers of the false tendon of the beef heart by means of triiodothyronine (T) and 2 4 dinitrophenol (Figs 1 3)

Incidence

Clinical electrical alternans is rare Hamburger Katz and Saphir had seen only one example of electrical alternans of the ventricular complex in a series of 10 000 electrocardiograms over a period of 13 years. However after the appearance of the first case 3 additional cases were reported within a short time suggesting to us that examples may be easily overlooked unless one becomes alternans conscious Kalter and Schwartz reported its occurrence in *1 out of 1 212* patients although these authors also suggested that more cases would be found if careful scrutiny were made particularly of multiple precordial leads. However Curran in 1961 reported that in reviewing 72 000 consecutive electrocardiograms in one hospital he found only 10 cases of electrical alternans.

Since Lewis first report of clinical electrical alternans in 1910 a total of 72 cases of this phenomenon has been reported to date In the vast majority of cases about 75 per cent the alternation was associated with a normal sinus rhythm and in a lesser number about 20 per cent with paroxysmal tachycardia In the remainder of the cases it has been reported to be associated with atrial flutter and fibrillation[6] Of 46 cases mentioned by Kalter and Schwartz,[7] 9 were recorded during attacks of paroxysmal tachycardia and 1 was recorded shortly after an attack had subsided.

Alternation of the T wave is the most common both clinically and experimentally Alternation limited to the P deflection is rare it has been mentioned only twice in the literature, once with drug intoxication *(propylthiouracil) and again* in primary amyloid degeneration of the heart.[11] Isolated alternation of the QRS complex is also rare Total alternans, namely simultaneous alternation of the atrial and ventricular deflections, was first reported by McGregor[12] and to date there are 16 cases described in the literature

Conditions associated with electrical alternans

Electrical alternans has been observed in patients during bouts of paroxysmal tachycardia particularly paroxysmal atrial tachycardia. It has been provoked by acute coronary occlusion in human beings[13] and after experimental ligation of a coronary artery in dogs.[1] It has also been encountered in valvular heart disease particularly aortic valvular stenosis,[14] and in pericarditis with effusion.[15,16] Clinically a number of drugs such as digitalis and propylthiouracil both in toxic doses, have initiated this phenomenon[16] Experimentally many agents such as glyoxylic acid[1] *EDTA (Fig 4)[1] aconitine[19] epinephrine* and L thyroxine[4] have produced it Electrical alternans has also been associated with primary amyloid degeneration of the heart.[1]

Significance

Electrical alternans may be transient recurrent, or permanent. When it accompanies rapid heart action as in paroxysmal atrial tachycardia it is usually of little significance. Occurring with a *slow heart* rate it is often a sign of organic heart disease When it persists at slow rates, the prognosis is usually poor[14] When electrical alternans appears in patients with pericardial effusion the underlying cause is, as a rule a serious disease of the pericardium most commonly neoplastic metastasis or tuberculosis with an excessive accumulation of fluid[1] Strom[1] *found 12 published* cases of electrical alternans combined with malignant disease of the pericardium and hemopericardium to which he added a case of his own

Mechanism

The exact mechanism which underlies the various forms of electrical alternans is still obscure A number of theories have been advanced to explain the phenomenon. The most popular theory predicates a prolongation of the refractory phase in some portion of the heart so that after activation a subsequent normal impulse finds

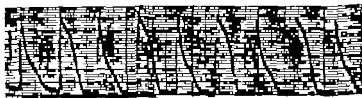


Fig 1 Electrical alternation of the transmembrane action potential of the single fiber of the left ventricle of the isolated perfused rabbit heart recorded by means of an intracellular electrode The alternation occurred spontaneously and was elicited 72 minutes after the tissue was placed in perfusion bath. Time lines, 0.04 sec gain 1 0 cm = 50 mv Dotted lines indicate zero level of potential

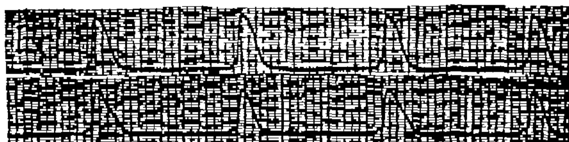


Fig 2 Electrical alternation of the transmembrane action potential of the atrial portion of the atrioventricular node in the isolated perfused rabbit atrium 12 minutes after 1.0 mg of triiodothyronine (T) was administered to the bath A Control. B T elve minutes after administration of T The initial step in the beginning of depolarization suggests that the action potential was taken in the atrial portion of the A-V node. The tissue as driven t fixed rate by Grass stimulator S indicates the point of stimulation. Time lines zero level of potential, and gain as in Fig 1

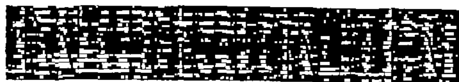


Fig 3 Electrical alternation of the transmembrane action potential of the Purkinje fiber of the f lse tendon of the beef heart produced by means of 2 4 dinitrophenol (5×10^{-4}M). The alternation in ol es the rat of repolarization ithout any pparent change in the rate of depolarization or magnitude of the action potential. S indicates the point of timulation provided by Grass stimulator as in Fig 2 Time lines and gain as in Fig 1



Fig 4 Lead II in he rabbit after the injection of EDTA (50 mg /kg) int the marginal ein of the ear Time of administration was less than 50 seconds. Time lines 0 04 sec. gain 2.0 cm = 1 m 1 Control. B During administration of EDTA. C, Immediately after injection electrical alternation of the T wa is presen D Forty seconds after no evidence of electrical alternation. E Ninety seconds after entricular fibrilla ion. (From Klemf M and Gross American Journal of Physiology 187 479 1956.)



Fig. 5. The effect of [illegible] of 0.5 mg. of [illegible] into the left branch of the aorta of the [illegible] heart. Alternation of the T wave [illegible] in the indirect bipolar electrogram [illegible] but not in the [illegible] action potential (lower record). Time lines 0.04 sec.; [illegible] 0.7 [illegible] = 50 m[illegible] for transmembrane potentials; for indirect electrograms 0.5 cm = 1 m[illegible].

that region of the myocardium still refractory. Consequently, the response of every alternate beat will be different electrically or mechanically from a previous beat. Brody and Rossman[3] postulated that electrical alternans may be the result of two alternating foci of impulse initiation or of two alternating paths of conduction from one focus. In essence, their postulation incorporates the concept of prolongation of refractoriness of a region of the heart muscle. The demonstration by us of electrical alternans in single myocardial fibers of both intact frog hearts and isolated perfused rabbit hearts militates against the general hypothesis that a portion of the myocardium is refractory in alternate beats. Hoffman and associates suggest that electrical alternation is related to the behavior of individual fiber membranes rather than to an alternating refractoriness of some myocardial cells. This suggestion was derived from their studies on the guinea pig ventricle using the intracellular electrode for the recording of electrical potentials in single fibers. Each fiber in the guinea pig ventricle from which electrical events were recorded by them showed action potentials with each beat. Therefore they considered it unlikely that some myocardial fibers take part in every second beat only and are refractory during the alternate cycle. Moreover, the concept of prolongation of refractoriness in a region of cardiac muscle is inadequate to explain total electrical alternans as observed in some patients with pericardial effusion. In view of this, McGregor and Baskind[24] proposed a theory involving a change in cardiac position to explain total electrical alternans. In the presence of a pericardial effusion, which is commonly associated with this type of alternation, a rotatory pendular movement of the heart can occur as a result of an unusual degree of freedom from the normal mediastinal and pulmonary restraints. When the oscillation bears a 1:2 ratio to the heart rate, an alternating difference in cardiac position becomes manifest in total electrical alternans. It has been repeatedly observed that the electrical alternans disappears immediately after pericardiocentesis.[17] The theory is not offered to explain instances of electrical alternans not associated with pericardial effusion.

On the basis of the present clinical and experimental data, there is no a priori reason to assume that a single mechanism is responsible for the initiation of this phenomenon. The occurrence of electrical alternans in single myocardial fibers strongly suggests that alternation in the rate and extent of electrolytic transfers across the myocardial membrane is involved.

Relationship to mechanical alternans

In spite of extensive investigations, considerable controversy exists in regard to the occurrence of electrical alternation without mechanical alternation and vice versa. It has been postulated by a number of investigators[22,23] that although portions of the heart muscle may be in a state of diminished excitability which leads to alternation that can be recorded mechanically, it may not be recorded electrically because these portions are not favorably placed for electrocardiographic recording or their effects may be masked by electrical forces in other regions of the heart. On the other hand, the summation of effects in diseased areas may preclude the observa-

tion of mechanical alternation yet the portion of the damaged muscle may be favorable for electrical recording Kisch[22] has postulated that both electrical and mechanical alternans are indicative of the same mechanism brought about by a regular change in the bioenergetic behavior of the heart after muscular contraction He attributes isolated electrical alternans to the electrical activity of the most external portion of the myocardium by stating that in the electrocardiogram the portion of the complex from the peak of the R to the end of the T wave is dependent only or predominantly upon activity in that portion He reasoned that electrophysiologic abnormalities which are restricted to the outer layer of the myocardium and which produce an electroradiographic alternation are not always sufficient to change the heartbeat or pulse wave similarly If Kisch is correct in limiting the origin of isolated electrical alternans to the most external layer of the heart muscle it may be stated from our experiments (Fig 5) that not all fibers in this area which are probed by the microelectrode necessarily participate in this phenomenon. Moreover Hogancamp and associates reported that in their experiments on the guinea pig ventricle, electrical alternans was displayed by only one third to two thirds of the cells punctured in any single heart In the same study the authors observed that electrical alternation of a single cell was never recorded in the absence of an associated mechanical alternation of the ventricular strip registered by means of a strain gauge The relationship appeared to be concordant in all cases, that is, the lesser action potential was associated with the weaker ventricular contraction In our studies the weaker ventricular contraction as observed in the frog muscle strip was associated with a shortened duration of the action potential (Fig 6) However mechanical alternans was seen several times without electrical alternans. Hogancamp and associates speculated that the alternation in action potentials would have been found had it been possible to record from a sufficient number of myocardial fibers. But, in view of the technical difficulty involved in setting up this type of experiment this will probably remain a matter of speculation.

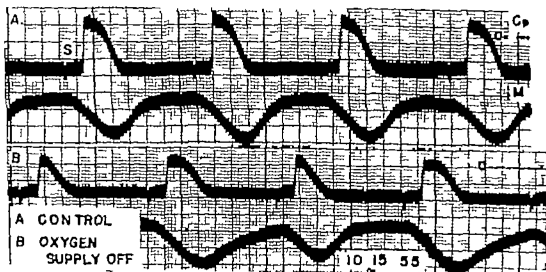


Fig 6 Effect of [illegible] on the electrical and mechanical activity of the isolated ventricular strip of the frog heart A Control record The heart muscle was driven by Grass stimulator at fixed rate of 40 beats per m[illegible] S indic[illegible] the point of stimulus. *C* is the single fiber membrane action potential which was simultaneously recorded with the isometric tension indicated by *M* below *B* Record taken 2 minutes after the supply of [illegible] shut off [illegible] the perfusate The [illegible] te is the same as in the [illegible] of record. There is alternation [illegible] both the membrane action potentials and the isometric tension record. The [illegible] contraction is associated [illegible] the shortened duration of the action potential. (From Kleinfeld Magi and Stein American Journal of Physiology 187 139 1956.)

Summary and conclusions

Clinical electrical alternans is a rare electrocardiographic abnormality. Since Lewis' first report of electrical alternans in a human being in 1910,[2] there has been a total of 72 cases of this phenomenon reported to date. In the vast majority the alternation was associated with a normal sinus rhythm and in a lesser number with paroxysmal tachycardia. Alternation in the form and magnitude of deflection, in the duration of intervals, or combinations of the two have been reported. Total electrical alternans that involves atria and ventricles has been consistently observed in the presence of pericardial effusion. Isolated electrical alternans has been associated with such conditions as acute coronary occlusion, drug intoxication, valvular heart disease, and primary amyloid degeneration of the heart. The phenomenon may be transient, recurrent, or permanent. When it accompanies rapid heart action as in paroxysmal atrial tachycardia, it is usually of little clinical significance. Occurring with a slow heart rate, it is often a sign of organic heart disease, and when it persists at slow rates the prognosis is usually poor.

Experimentally, electrical alternans has been produced in both contractile and conductive fibers in a number of species. The phenomenon was usually transitory, unrelated to heart rate, and more often than not associated with decreased cardiac contractility. Four types were observed: alternation in (a) the rate of depolarization, (b) the rate of repolarization, (c) the magnitude of the action potential, and (d) hyperpolarization. The alternation in the rate of depolarization and in the rate of repolarization of the action potential correlated with the electrical alternans of the QRS complex and T wave, respectively.

The available data do not permit the formulation of a single hypothesis to explain the various forms of electrical alternans described. The experimental demonstration of electrical alternans in single cells of intact hearts militates against the general hypothesis that a portion of the myocardium is refractory in alternate beats. The hypothesis also does not explain total electrical alternans seen in cases of pericardial effusion. Observations in single cells strongly suggest that alternation in rate and extent of transport of ions across the myocardial membrane is involved.

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Quantitation of valvular insufficiency in man by angiocardiography

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To date, there has been no satisfactory method for quantifying mitral or aortic valvular regurgitant flow in man with valvular heart disease. Angiocardiography and cineangiocardiography have been applied to give qualitative data on regurgitant flow,[1-3] and various methods have been described for analyzing the slopes of indicator-dilution curves to gain quantitative information about regurgitant flow.[4-6] However, the extent to which reliable regurgitant flow values can be obtained by these techniques is doubtful and the theory on which they are based has been criticized.[6,7] Warner[7] has recently reviewed the use of indicator-dilution techniques with differing sites of injection and sampling for the quantification of regurgitant flow.

Arvidsson[8] has utilized biplane angiocardiography to determine left atrial volumes and volume curves as well as changes in left ventricular volume in subjects with differing types of mitral valvular disease. It is the purpose of this paper to describe a clinically applicable method for quantifying aortic and mitral valvular regurgitant flow that is based on a comparison of left ventricular stroke volume as determined by an adaptation of biplane angiocardiography with forward flow determined by the Fick or indicator-dilution techniques. The data in the present study have been reported in part, in preliminary form.[9]

Methods

Thirty-seven patients with valvular heart disease and murmurs suggestive of the presence of aortic or mitral valvular insufficiency were studied in the recumbent, postabsorptive state after premedication with 0.1 Gm. of pentobarbital. Catheterization of the right side of the heart was performed through an antebrachial vein and cardiac output was determined in duplicate by the Fick method or an indicator-dilution technique with Evans blue dye and with pulmonary arterial injection and brachial arterial sampling. Details of these methods as used in this laboratory have been described previously.[10] Oxygen content of the samples of blood was determined by the manometric method of Van Slyke and Neill.[11] Heart rate was re-

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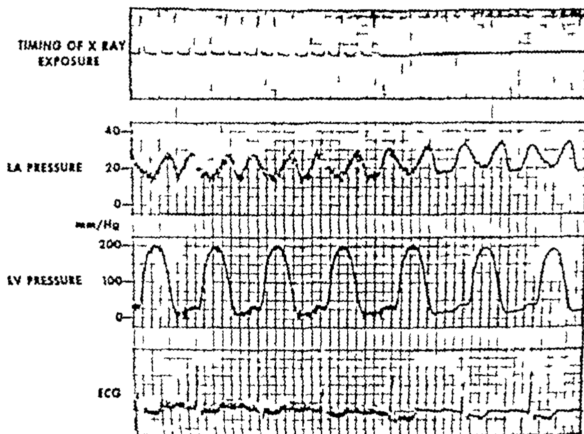


Fig 1 Time of [illegible] posure is ill st ted with respec to left trial nd left entricular pressures nd the lec n rd gr m

corded during e ch leter i tion of car diac output nd mean fl w per stroke was calcul ted When rdiac outputs were detern ined by both the Fick and i lu ator dilution methods flow per stroke was calculated as a mean of flow per troke determ ned by these two ethods.

After catheterization of the right side of the heart all but o subject underwent catheterization of the left side of the heart by one or more of the following methods transseptal[12] retrograde aortic or trans bronchial. Subjects who underwent trans-bronchial catheterization received addi tional premedication with meperidu e 25 to 50 mg and scopolamine 0 3 mg With the transbronchial method observations of pressure were made through a poly ethylene catheter after remo al of the bronchoscope and transbronchial needle. Determ nation of cardiac output by the indicator-dilution techni que was perforn e l at the time of catheterization of the left side of the heart. Pressures recorded during catheterization of the left side of the heart were used in calculating the valve orifice areas listed in Tables I a d II

I mediat ly aft r the precedin studies angiocardiogr phy was performed with a power injector d livering 4 to 6 Kg of pressure per square centimeter Fifty milliliters of 0 per cent sodiu acetri zoate* w s injected into either the right atrium or pul ionary artery in 20 sub-jects. I 11 subjects 40 ml. of 75 per cent H paque† was injected into the left entricle after retrograde catheterization of the aorta from a radial or fer oral artery In 6 subjects, 50 ml of 75 per cent Hy paque was injected into the left atrium through a vinyl catheter introduced over a transseptal needle

Biplane x-ray films were taken in the anteroposterior (A P) and left lateral pro-jections with a Schona ider biplane film cha ging u it t 4 per second n 16 sub-

*Urokon, Mallinckrodt Chemical Works, St. Louis, Mo.
†Winthrop Laboratories, New York, N Y

jects and at 6 per second in the remainder of the subjects. X-ray exposures were 300 to 400 Ma. 100 to 120 kv and 1/20 to 1/30 second. In all subjects the timing of each film exposure with respect to the electrocardiogram and intra-arterial or intracardiac pressures was recorded by a photocell[14] as illustrated in Fig. 1. Subjects who developed a persistent arrhythmia at the time of injection of contrast material were not included in this study.

Left ventricular volumes and changes in volume were calculated from the biplane x-ray films. On each film the margins of the opacified left ventricular chamber were traced and the enclosed area was determined by planimetry. The maximum length of the chamber was measured on each film and transverse chamber diameters were calculated using the formula for the area of an ellipse

$$d = \frac{4A}{\pi l} \qquad (1)$$

where d is the calculated transverse diameter, A is the planimetered area, and l is the measured length. Each length and diameter was corrected for distortion from the nonparallel x-ray beams resulting from the short x-ray tube-to-film distances. The method used in correcting for x-ray distortion has been described in detail elsewhere. This method requires knowledge of x-ray tube-to-film distances and central x-ray beam-to-film relationships which were measured directly. The distances from left ventricle to film can be determined from the biplane films.

After correction for x-ray distortion, chamber volumes were calculated by using an ellipsoid formula and applying the "longest measured length" method as previously described

$$V = \frac{4}{3} \cdot \pi \cdot \frac{d}{2} \cdot \frac{d_1}{2} \cdot \frac{lm}{2} \qquad (2)$$

where V = volume in cubic centimeters, d and d_1 are the transverse diameters in centimeters calculated from the A-P and lateral films respectively, and lm is the longest measured length in centimeters, whether in the a-p or lateral film. This method for calculating left ventricular chamber volume has been tested by taking biplane x-ray films of postmortem human hearts distended with known volumes of contrast material and relating calculated to known volumes.[18] These earlier studies established a regression equation and standard error of estimate for this method. This regression equation was applied to adjust the volumes calculated by Formula 2

$$V' = .928\ V - 3.8 \qquad (3)$$

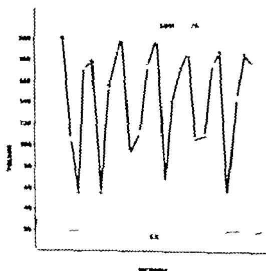


Fig. 2. Left ventricular volume observations are plotted with respect to time of film exposure.

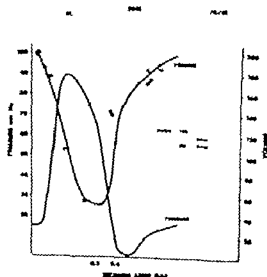


Fig. 3. Volume observations in Fig. 2 are plotted with respect to the time of the heart cycle, and a single composite volume curve is constructed. As indicated, left ventricular stroke volume is 146 c.c., forward flow is 33 c.c. per beat, and regurgitant flow is 113 c.c. per beat.

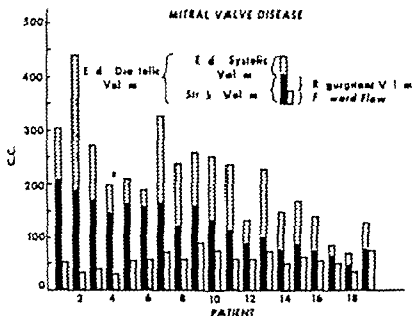


Fig. 4. Left ventricular volume observations in subjects with mitral valvular disease. In subjects indicated by an asterisk, calculated valve areas were related to valve findings at operation or autopsy.

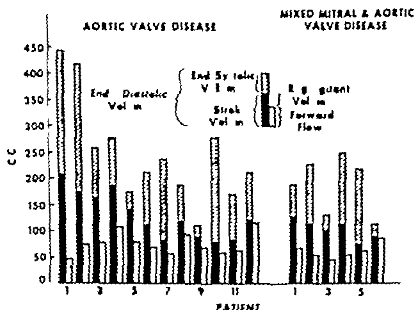


Fig. 5. Left ventricular volume observations in subjects with aortic and mixed mitral and aortic valvular disease. In subjects indicated by an asterisk, calculated valve areas were related to valve findings at operation or autopsy.

where V' = volume in cubic centimeters adjusted by the regression equation and V = volume calculated by Equation 2.

The volume calculated from each set of films was plotted with respect to the time of the heart cycle to construct a left ventricular volume curve as shown in Fig. 2. Because the relatively slow rate of filming permitted relatively few observations on volume during any single beat, each calculated volume was plotted with respect to the time of the heart cycle by

relating it to the QRS of the electrocardiogram. In this manner volumes calculated from 3 to 5 heartbeats were combined to construct a single composite volume curve as illustrated in Fig. 3. The curve is drawn to represent an average of the calculated volumes. Usually there were multiple observations at end-diastole and end-systole, as illustrated. Left ventricular stroke volume was calculated as the difference between end-diastolic and end-systolic volumes. Occasionally because of a rapid ventricular rate, or because the rate of filming was relatively synchronous with the heart rate no films were taken at end-systole or end-diastole and left ventricular stroke volume was indeterminate.

In subjects with atrial fibrillation and

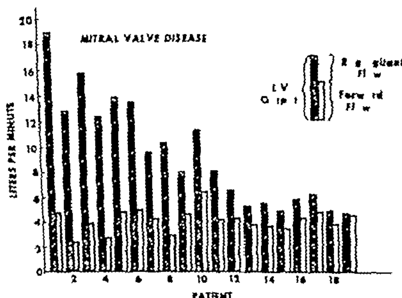


Fig. 6. Left ventricular minute output, forward flow and regurgitant flow in subjects with mitral valvular disease.

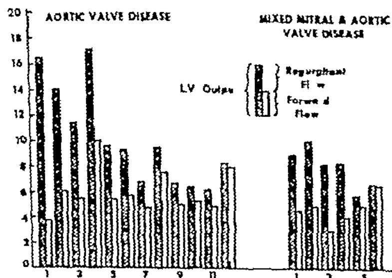


Fig. 7. Left ventricular minute output, forward flow and regurgitant flow in subjects with aortic and mixed mitral and aortic valvular disease.

a rapid ventricular rate or marked irregularity of the ventricular rate the beat-to-beat variations of end-systolic end-diastolic and stroke volumes may make difficult or impossible the construction of a composite ventricular volume curve and determination of a mean left ventricular stroke volume. Data from such subjects were not included in the study. Subjects with atrial fibrillation who were included in this study had during x-ray filming a slow or relatively regular ventricular rate which reduces the beat-to-beat variations in volume. In these subjects, left ventricular volume curves and stroke volumes were determined by beat-to-beat analysis of at least three beats during the period of filming, and the average of these values was taken to represent mean left ventricular stroke volume.

Aortic or mitral valvular regurgitant flow was determined by relating mean left ventricular stroke volume calculated from the angiocardiograms to mean forward flow per stroke determined by the Fick or indicator-dilution methods. Cardiac output determined by the Fick method provides a measure of mean flow rate that is independent of aortic or mitral valvular insufficiency. Cardiac output determined by the indicator-dilution method relates the quantity of indicator injected to the time-concentration distribution of this substance at a sampling site. Although valvular regurgitation may alter the time-concentration characteristics, a reliable measurement of forward flow is still obtained. This has been checked experimentally in models by Korner and Shillingford and others. As can be seen in Table I measurements of cardiac output by the Fick and indicator-dilution methods showed close agreement in this study. In the presence of competent valves the forward flow (FF) cubic centimeters per beat as determined by the Fick or indicator dilution methods should equal left ventricular stroke volume (LVSV). In earlier studies by Arvidsson[1] and also in studies in this laboratory[10] stroke volumes determined by angiocardiography show close agreement with stroke volumes determined by the Fick or indicator-dilution methods in subjects without valvular insufficiency or arrhythmias. In the presence of incompetence of either the mitral and/or aortic valves regurgitant flow (RF) is expressed by Formulas 4 and 5 (*shown at bottom of page*). Application of these methods to the study of an individual patient is illustrated in Fig. 3.

Valve areas were calculated as indicated in Tables I and II by using the formulas as described by Gorlin and co-workers[7]: Formula 6 (*shown at bottom of page*) where MVF = mitral valve flow in diastole and PG = mean pressure gradient across the mitral valve in diastole and Formula 7 (*shown at bottom of page*) where MVF = systolic mitral valve flow and PG = mean systolic pressure gradient across the mitral valve. Formula [illegible] was also used to calculate aortic systolic and diastolic valve areas. In these calculations, mean aortic valve flows and mean pressure gradients between the left ventricle and aorta were used during systole and diastole respectively. Mitral diastolic valve flow was considered to be equal to left ventricular stroke volume, and mitral systolic flow to be equal to left ventricular stroke volume minus forward flow in subjects with mitral valvular disease. For subjects with aortic valvular disease left ventricular stroke volume and stroke volume minus forward flow were considered to be equal to aortic systolic and diastolic

$$RF\ c.c./beat = LVSV\ c.c./beat - FF\ c.c./beat \qquad (4)$$

$$RF\ c.c./min = RF\ c.c./beat \times heart\ rate/min \qquad (5)$$

$$\text{Diastolic mitral valve area in cm}^2 = \frac{MVF}{31\sqrt{PG}} \qquad (6)$$

$$\text{Systolic mitral valve orifice in cm}^2 = \frac{MVF}{44.5\sqrt{PG}} \qquad (7)$$

valve flows respectively This method does not permit separate quantitation of aortic and mitral regurgitant flows when both are present. In subjects with these two lesions, a total regurgitant flow is calculated and it is not possible to calculate valve orifice sizes. The calculated valve orifice areas were related to valve orifice sizes as estimated at the time of operation or as measured at autopsy Post mortem measurements were made on a pulse duplicator in Patient W W of Table II

Results

The data from 37 subjects with mitral and or aortic valvular disease included in this study are listed n the tables with the clinical diagnosis Subjects with a history of heart failure as manifest by peripheral or pulmonary edema are indicated by *CHF* Table I includes subjects with mitral valvular disease Table II subjects with aortic valvular disease and Table III subjects with mixed lesions of both the aortic and mitral valves. Figs 4 and 5 illustrat graphically the end-diastolic end-systolic and stroke volumes together with the forward flow and regurgitant flow per beat in these subjects. Figs. 6 and 7 illustrate graphically left ventricular minute output and regurgitant flow in the same subjects.

In all but one subject (Patient L.C of Table III) left ventricular stroke volume exceeded forward flow with values for regurgitant flow as high as 161 c c per beat (R B Table II) Eight subjects with mitral valvular disease and 5 subjects with aortic or mixed m t al and aortic valvular disease had values for regurgitant flow that exceeded forward flow Regurg tant flow was as high as 14 2 l ters per m nut and left ventricular minute output was as high as 19 l ters per minute as can be seen in Figs. 6 and 7 Large left ventricular minute outputs were seen in subjects with and w thout a history of hea t failure

Subjects with the larger values for re gurg t t flow had large left ventricular end-diastolic volu nes. In th 12 subjects w th n t l egurg tant flow values of 55 per beat or greater left ventricular end-dia tolic volume exceeded 190 c.c. in all subjects, and exceeded 200 c.c in all but one subject Subjects with aortic regurgitant flow values of 40 c.c per beat or greater had end-diastolic volumes in excess of 175 c.c Of those subjects who had mixed mitral and aortic valvular disease and regurgitant flow of more than 50 c.c per beat all but one (W I Table II) had left ventricular end-diastolic volumes n excess of 190 c c However not all subjects with large left ventricular end diastolic volumes had large regurgitant flow values, indicating that factors in addition to the volume of regurgitant flow played a role n elevating the left ventricular end-diastolic volume.

Left ventricular end-systolic volume as ndicated in Tables I II and III and illustrated by the length of the cross-hatched bars in Figs. 4 and 5 showed considerable variation from subject to subject Subjects with the largest regurgitant flow values tended to have the larger end systolic volumes but as can also be seen from these figures, the end-systolic volume was not directly related to the egurgitant volume This suggests that factors other than the volume of regurgitant flow per se were of importance in determin ng ventricular end-systolic volume. Indeed the majority of subjects with large end-systolic volumes had a history of heart fa lure or were in heart failure at the time of the studies.

To test this method for determining left ventricula stroke volume and regurgitant volume it has been possible to relate aortic and mitral valve areas as calculated from the determined flow and pressure values to findings at the t me of operation or at autopsy in 15 subjects with m tral or aortic valvular disease These results are also ndicated n the tables. As can be seen the calculated valve areas showed close agreement with findings at operation or autopsy in each case

Discussion

The method described here for determ n ing mitral or aortic regurgitant flow depends on measurement of the difference between left ventricular stroke volu ne and forw rd flow per beat Left ventricular volumes are calculated from biplane angiocardiograms of the opacified left ventricular

Table I Mitral valvular disease

Patient		Diagnosis	Fick cardiac output c.c./min.	Fick cardiac output Heart rate/min.	Dye cardiac output c.c./min.	Dye cardiac output Heart rate/min.	Heart rate at angio
1	W I	RHD with MS MI AF CHF	4 610	92	4 860	87	91
2	C S	RHD with MI MS AF CHF	2 160	63	2 150	57	68
3	I M	MI NSR CHF	4 380	108	4 610	108	93
4	J M	MI NSR CHF	3 130	90	2 900	J0	85
5	D F	RHD with MI MS AI CHF			4 800	8	83
6	M N	RHD with MI MS NSR CHF	5 100	85	4 740	82	85
7	H S	RHD with MI MS AF CHF	3 [illegible]00	54			57
8	H I	RHD with MI MS AF CHF			2 900	78	62
9	K A	RHD with MI MS, NSR CHF	4 [illegible]90	49	4 660	53	50
10	S J	RHD with MI MS NSR CHF			6 400	82	83
11	Q A	RHD with MI MS NSR CHF	5 120	84	5 330	90	70
12	R F	RHD with MI MS AF CHF	4 060	6	4 440	78	71
13	C R	RHD with MI MS AF CHF	3 040	48	3 760	44	51
14	W C	RHD with MI MS NSR O	4 140	81	4 150	80	71
15	G N	RHD with MS, MI AF CHF	3 590	58	4 340	68	55
16	V I	RHD with MS MI AF CHF	4 100	69	3 780	69	73
17	E S	RHD with MS MI NSR CHF	4 210	83	4 540	90	93
18	J F	RHD with MS NSR CHF	3 610	102	4 230	96	100
19	B H	RHD with MS NSR CHF	5 300	66	4 900	66	59

Mitral insufficiency [illegible] ruptured chordae tendineae
†Ruptured chordae tendineae with large regurgitant flow. Surgeon felt large regurgitant jet, but could not estimate [illegible]
RHD Rheumatic heart disease MS Mitral stenosis MI Mitral insufficiency AF Atrial fibrillation CHF Congestive heart failure [illegible]

chamber and left ventricular stroke volume is determined as the difference between mean end-diastolic and mean end systolic volume of the 4 to 5 heartbeats which occur during angiocardiography Mean forward flow per beat is determined as the quotient of the minute output measured by the Fick or indicator-dilution method divided by the heart rate. In other studies in this laboratory left ventricular stroke volumes calculated from biplane angiocardiograms after the injection of contrast material into the right atrium or the pulmonary artery have agreed closely with stroke volumes determined by Fick and indicator-dilution techniques in subjects without clinical evidence of valvular insufficiency or arrhythmias.[8] Arvidsson[1] has reported similar results in comparing mean stroke volumes determined by the Fick method with left ventricular stroke volumes calculated from biplane angiocardiograms after both right-sided and left-sided injections of contrast material.[1]

This quantitative angiocardiographic method requires films that demonstrate an opacified left ventricle with margins that can be defined and traced In subjects with large volumes of regurgitant flow right atrial or pulmonary arterial injection of contrast material often resulted in films with such poor opacification of the left ventricle that calculations of volume were not possible Left atrial or left ventricular injection of contrast material gives much better left ventricular opacification however marked opacification of an enlarged left atrium may obscure a portion of the left ventricle. Furthermore selective injection of contrast material into the left

elevated pulmonary wedge pressure by cardiac catheterization. If at the same time a normal left atrial pressure can be obtained this is diagnostic for the disease. In any case in which cor triatriatum is suspected a cardiotomy should be attempted with the purpose of correcting it surgically. This may be a lifesaving procedure.

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LV volume			*Mean forward flow* (c.c./beat)	*Regurgitant flow*		*Total LV output* (L./m)	*Mitral valve area*	
EDV	*ESV*	*LVSV*		*c.c./beat*	*L./min.*		*Calculated* (cm)	*Measured* (cm)
305	96	209	53	156	14.2	19.0		
440	250	190	36	154	10.5	12.9		
							Systolic	
273	103	170	42	128	11.9	15.8	2.9	3.0–3.5
200	54	146	33	113	9.61	12.4	1.9	†
212	48	164	57	107	9.10	13.9		
191	32	159	59	100	8.50	13.5		
							Diastolic	
329	162	167	74	93	5.30	9.52	2.2	2.0
							Diastolic	
240	115	125	37	88	7.22	10.25	2.10	2.0–2.5
260	100	160	92	68	3.40	8.00		
253	118	135	77	58	4.81	11.2		
237	122	115	60	55	3.85	8.05		
							Diastolic	
135	44	91	61	30	2.13	6.46	1.8	1.5–1.8
							Diastolic	
230	127	103	74	29	1.48	5.25	2.4	2.5–3.0
149	71	78	52	26	1.85	5.54		
							Diastolic	
169	80	89	64	25	1.38	4.90	1.0	0.9
141	64	77	57	20	1.5	5.78	0.6	0.5–0.75
87	20	67	52	15	1.40	6.23	1.2	1.0
72	23	49	37	12	1.12	4.90	0.8	0.8–1.0
130	50	80	77	3	0.18	4.72	1.1	1.3

NSR Normal sinus rhythm. LV Left ventricle. EDV End-diastolic volume. ESV End-systolic volume LVSV Left ventricular

heart, and in particular the left ventricle may induce premature contractions and arrhythmias. Such induced arrhythmias are undesirable in applying these methods, since the heart rate and ventricular pressure at the time of angiocardiography must be comparable to the rate and pressure at the time of the determination of forward flow if volumetric data obtained at these two times are to be related Untoward cardiovascular reactions to angiocardiography observed in this study were similar to those described by others and consisted of premature contractions, paroxysmal tachycardia bradycardia and hypotension [31,32] Subjects in whom these occurrences were persistent or marked were not included in this study

In subjects with atrial fibrillation and beat to-beat variations of left ventricular filling and ejection the application of these methods as a quantitative tool has shortcomings. If the ventricular rate is slow and the rhythm reasonably regular a satisfactory composite volume curve can be constructed Because of this, it is helpful to attempt to achieve a slow ventricular rate with digitalis and treatment of heart failure prior to study in subjects with atrial fibrillation If the ventricular rate is rapid and the rhythm irregular the beat-to-beat variations of end-diastolic, end-systolic, and stroke volumes[33] may make it difficult if not impossible to determine from the angiocardiograms a mean stroke volume that can be compared with the forward flow value derived from the Fick and indicator-dilution methods. This problem of determining a mean stroke volume is due in part to the limitations imposed by the

Tab II Aortic valvula disea e

Pat nt	D e	F k rdiac output L/m	Hea t rate/m	Dye rdia output L/m	Heart rate/m	Heart rate at D
1 R K	AI SBE NSR CHF	8 80	8	3 530	6	79
2 W W	RHD th AI AS NSR CHF			6 830	80	80
3 R K	RHD b AI AS NSR	5 180	62	5 540	0	70
4 J H	RHD b AI AS NSR	8 60	80	9 350	79	92
5 W I	RHD ib AS AI NSR	5 110	64	5 410	66	68
6 I W	RHD b AI NSR	5 80	75			82
R	ASHD AI NSR CHF	5 390	97	5 250	86	83
8 I D	RHD MS AI NSR	7 412	79	7 200	74	80
9 J A	RHD b AS AI NSR	4 40	70	4 770	68	1
10 I B	RHD th AS AI NSR CHF	4 650	8			84
11 M	RHD th AS AI NSR	4 940	6			82
12 H C	RHD th AS AI NSR	6 830	58			68

Fewer m of aortic alve
Determined pulse displacement
AS Aortic valvular stenosis AI Aortic valvular insufficiency SBE Subacute bacterial endocarditis Other abbreviations are as in

Tabl III Mixed m t al and aortic val ula disease

P tient	Diagn	Fick rdiac output L/m	Hea t rate/m	Dye rdiac output L/m	Heart rate m
1 J J	RHD nb MS AS AI NSR CHF	5 400	78	4 530	71
2 O K	RHD ib MI MS AI AS NSR CHF	4 290	78	5 240	92
3 G D	RHD nb MS MI AS AI NSR CHF	4 210	88	4 450	90
4 C S	RHD ib MI MS AI AF	4 120	71		
5 O C	RHD nb MI MS AI AF CHF	4 650	69	4 150	67
6 L C	RHD nb MS MI AI NSR	7 610	86	7 510	86

Abbreviations are as in Tables I and II

angiocardiographic equipment which permits only a limited number of observations over a relatively few heartbeats

Subjects with the more marked degrees of mitral and or aortic valvular regurgitant flow had left ventricular end-diastolic volumes that were usually in the range of 200 c.c. or greater Left ventricular end diastolic volumes determined by these same methods in 23 subjects without clinical evidence of left ventricular disease or valvular insufficiency were 100 ± 25 c.c.[34]

Thus these subjects with valvular insufficiency had left ventricular end-diastolic volumes that were nearly twice normal Arvidsson has also described elevated left ventricular end-diastolic volumes in subjects with mitral insufficiency In the present study subjects with mitral stenosis and only small volumes of regurgitant flow had in general relatively normal left ventricular end-diastolic volumes. This is of importance because it indicates that determination of left ventricular end

LV volume			*Mean forward flow (c.c./beat)*	*Regurgitant flow*		*Total LV output (L./m)*	*Aortic valve area*	
EDV	*ESV*	*LVSV*		*c.c./beat*	*L./m*		*Calculated (m)*	*Measured (cm ²)*
443	234	209	48	161	12 7	16 5	Diastolic 1 58	1 5–1 8
420	244	176	76	100	8 0	14 1	Systolic 1 5	1 5†
							Diastolic 0 8	0 7
259	95	164	79	85	5 95	11 5		
278	91	187	109	78	7 18	17 2		
177	33	142	81	61	4 15	9 66		
214	100	114	70	44	3 61	9 35	Diastolic 0 2	0 2
240	157	83	58	25	2 08	6 89		
188	69	119	95	24	1 9	9 3		
112	23	89	69	20	1 42	6 32		
280	200	80	60	20	1 68	6 72		
173	88	85	65	20	1 64	6 97		
213	91	122	118	4	0 27	8 3		

Table I.

Heart rate at angio	*LV volume*			*Mean forward flow (/beat)*	*Regurgitant flow*		*Total LV output (L./m)*
	EDV	*ESV*	*LVSV*		*/beat*	*L./min*	
69	191	62	129	67	62	4 28	8 90
88	228	113	115	56	59	5 19	10 1
80	133	30	103	48	55	5 20	8 24
74	250	137	113	58	55	4 07	8 36
76	221	144	77	65	12	91	5 85
75	115	26	89	88	1	08	6 68

diastolic volume per se is of some value in differentiating mitral stenosis from mitral insufficiency.

The large left ventricular end-diastolic volumes observed in this study were not confined to subjects with large volumes of regurgitant flow, nor was the end-diastolic volume directly related to the volume of regurgitant flow. In subjects with large stroke volumes and small end-systolic volumes the enlarged end-diastolic volume was probably a direct consequence of the regurgitant flow. However, individual subjects in each group and in particular those with aortic valvular disease had large left ventricular end-diastolic volumes with relatively small volumes of regurgitant flow and large end-systolic volumes. Left ventricular failure appeared to be the basis for the enlarged diastolic volumes in these subjects. Finally, in each group there were subjects with large regurgitant flow values and large end-diastolic and end-systolic volumes. The enlarged end-

diastolic volumes in these subjects probably reflect a degree of left ventricular decompensation combined with a large volume of regurgitant flow.

Despite the presence of congestive heart failure in many of these subjects with valvular insufficiency, left ventricular output was usually elevated and was occasionally markedly elevated. Large left ventricular output values in subjects with valvular insufficiency have been previously demonstrated by others using different techniques for estimating regurgitant flow. These data demonstrate that aortic or mitral valvular insufficiency results in a high output state from the standpoint of left ventricular function and in this regard simulates the situation found in the case of certain intracardiac shunts or arteriovenous fistulas.[9]

The method described here does not differentiate between the aortic or mitral insufficiency, nor does it permit separate determination of the volume of aortic and mitral regurgitant flow in subjects with both lesions. However, it does provide a method for determining left ventricular stroke volume in subjects with both mitral and aortic valvular insufficiency. The calculated regurgitant flow value reflects the difference between left ventricular stroke volume and forward flow per stroke without regard to whether the aortic or the mitral valve is insufficient. Occasionally the site of insufficiency can be determined in a qualitative sense by observing the absence or presence and the degree of left atrial opacification after injection of contrast material into the left ventricle or left ventricular opacification after injection of contrast material into the aorta.

This is a clinically applicable method for determining left ventricular output and volume of regurgitant flow in subjects with aortic and or mitral valvular insufficiency. When the observations on flow are combined with the observations on pressure it is possible to calculate the size of the orifices of diseased valves. The validity of the flow values determined by this method is supported by the close agreement between valve orifice sizes calculated from the flow and pressure observations in this study and the orifice sizes estimated at operation or measured at postmortem examination.

Summary

A method is described for quantifying aortic and or mitral valvular regurgitant flow. This method is based on a comparison of left ventricular stroke volume and forward flow per stroke. Left ventricular stroke volume is determined from biplane angiocardiograms. Cardiac output determined by the Fick or indicator-dilution method is used as a measure of forward flow. These techniques were applied to study 37 patients with valvular heart disease. Regurgitant flow values of three to four times forward flow were found in subjects with severe valvular insufficiency. In 15 subjects aortic or mitral valve orifice sizes as calculated from these data agreed closely with findings at operation or postmortem examination.

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Function of normal and hypertrophied hearts during perfusion of a main coronary artery with unsaturated blood or colloidal isotonic solutions at systemic pressures

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It is generally believed that sudden regional myocardial ischemia can produce fibrillation. This is thought to be due to the difference in oxygen tension of the ischemic and nonischemic region of the heart which is said to produce an electrical instability of the myocardium.[14] The danger of fibrillation can be reduced by diminishing the difference in oxygen tension between the two areas, by establishing arterial collateral communications between the ischemic and nonischemic zones.[29] The quantity of blood necessary to prevent the breakdown of electrical stability of the beating heart is believed not to be large and Eckstein and associates[3] have demonstrated that 4 c.c. of additional arterialized blood per minute delivered to the circumflex area prevented death within 1 hour after ligation of the circumflex artery.

On the other hand it has been observed that a uniformly anoxic heart produced by occluding the intratracheal tube for periods of 6 to 8 minutes is a relatively stable heart. Such a heart becomes extremely blue and fibrillates much later than does one in which a major coronary artery has been occluded. Studies of cyanotic patients have clearly shown however that the myocardium of the left ventricle is not seriously injured when the oxygen saturation of the blood of the coronary arteries is lower than that of the normal venous blood.[19] What happens when the *saturation of the blood of the coronary arteries of a circumscribed region of the heart has been decreased to the value of the venous blood?* When a coronary artery is supplied with venous blood at low pressures as in cases of congenital anomalous coronary arteries which originate from the pulmonary artery,[27] ischemic lesions of the myocardium are found. No information is at hand concerning *perfusion of a main coronary artery with venous blood at systemic arterial pressure.*

The sudden perfusion of a coronary artery with unsaturated blood should suddenly diminish the oxygen tension of the affected myocardium. Is this sudden local decrease in oxygen tension able to produce electrical instability with a resulting tendency to fibrillation? Or conversely would such hypoxia (being a strong vasodilator stimulus) dilate the coronary arteries and open the intracoronary anastomoses? On the basis of this latter assumption Lillehei and associates

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proposed to develop such anastomoses by decreasing the oxygen saturation of the arterial blood They produced small right to-left shunts by anastomosing the left atrial appendage to the pulmonary artery By this means, permanently functioning intracoronary channels were made.

In previous experiments we have shown that an abrupt infusion of unsaturated blood equaling 25 per cent of the weight of the heart, made directly into the right or left ventricular myocardium did not produce ventricular fibrillation [22] Even larger infusions of a solution of 6 per cent dextran (American type) in normal saline (1 000 ml in 10 minutes) did not produce fibrillation The sudden increase in myocardial pressure in a circumscribed region after such an nfusion of blood or dextran should theoretically decrease the oxygen tension This difference in oxygen tension of the myocardial tissues was insufficient to produce fibrillation Why this was so is difficult to explain but it may have resulted from the low oxygen tension provoking a strong vasodilator stimulus

The absence of information in the liter ature concerning cardiac function of normal and hypertroph ed hearts after regional perfusion of the coronary arteries with un saturated blood or normotonic colloidal solutions as for example dextran at a level of pressure equal to that n the sys temic arteries led to the present study

Methods

The first subject to be investigated is the functional changes of the *normal heart* after perfusion of the anterior descendi g coronary artery with unsaturated blood or dextran For this purpose 10 young mongrel dogs which weighed 16 to 20 kilograms were used. Anesthesia was in duced and ma tained with intravenous Nembutal Cyclic positi e pressure insuf flation of the lungs with room air was main tained and the thorax was opened through the fourth left intercostal space The left trium and descending aorta were ca nu lated through the femoral artery the cannulas bei g con ected to an electromanometer It is important at this stage to note the ariation n the coronary arteries of the 10 a imals studied The branches of the left anterior descending coronary artery were distributed predominantly in the left ventricle in 9 dogs (type A) and to both the left and right ventricles in 1 dog (type B) The angle between the circumflex and anterior descending coronary arteries was vasculari zed from a branch arising from the circum flex artery in 7 dogs, and from the anterior descending artery in 3 dogs. There were either 4 or 5 main branches of the anterior descending coronary artery supplying the left ventricle In all dogs the fourth left branch was prepared at the left border of the heart. After heparinization of the dogs (3 mg per kilogram) this branch was divided its central end ligated and its distal end left free to collect the backflow of the blood which was measured during the whole experiment. The minute back flow[23] was between 0 1 and 0 23 ml (aver age, 0 17 ml) and the oxygen content was 17 to 19 volumes per cent. The epicardium was then incised to the upper third of the anterior interventricular sulcus, and the anterior descending coronary artery was freed for 3 cm The distal part of the artery was cannulated with a 2 mm stiff catheter w th a terminal hole the catheter was in serted 2 cm distal to the bifurcation of the main artery and the artery was oc cluded centrally The catheter was in serted to a distance of 1 5 to 2 cm and the tip of the catheter was secured some milli meters distal to the first ma n left branch of the anterior descending artery the orifice of which was thus occluded by the side wall of the catheter The catheter was connected to a strain gauge and back pressure of the coronary artery was re corded These pressures were between 20 17 and 38/20 mm Hg (average 29 19 mm. Hg) (Fig 5,*A*) After occlusion of the descending artery the backflow decreased to 0 to 0 1 ml (Fig 4,*A*) the aortic pressure decreased by 10 to 20 mm Hg and the left atrial pressure increased 2 to 5 mm. Hg At this point, extrasystoles appeared (Fig 1) Heparinized venous blood (5 mg heparin per 1 000 ml. blood) obtained from the right atrium of donor dogs (the oxygen content of wh ch was about 13 volumes per cent, and the tem perature 20°C) was perfused at a systemic pressure level of about 130 mm Hg nto the distal part of the coronary artery

Fig 1 *1 9:00 A.M.* Normal aortic nd left trial pressures after the thora is opened *2 9:10 A.M.*—Oc lusion of the anterior descending coronary artery Anoxia of the myocardium Aortic pressure decreased Left atrial pressure increased *3 9:15 A.M.*—Unsaturated blood is perfused through the coronary artery at rat of 60 drops per min t *4 9:30 A.M.*—Perfusion of unsaturated blood is continued for 15 minutes. *5 9:45 A.M.*—Per fusion of unsaturated blood is ontinued for 30 mi utes. *6 9:46 A.M.*—Quick perfusion ithin 5 seconds t 1 minute of 20 of unsaturated blood. *7 9:50 A.M.*—Quick perf sion ithin 5 seconds to 1 minut of 20 .c of saturated blood *8 9:52 A.M.*—Perfusion of dextran at a rat of 60 drops per minute *9 10:07 A.M.*—Pe fusion of dextra is continued for 15 min tes *10 10:22 A.M.*—Perfusion of dextran i onti ued for 30 minutes. *11 10:24 A.M.*—Quick perfusion within 5 seconds of 20 .c of nsaturated blood *12 10:30 A.M.*—Quick perfusion within 5 seconds of 20 of normotonic saline solution. *13 10:35 A.M.*—Pressures 80 minutes fter perfusion.

(Fig 2) The perfusion rate was adjusted to a rate of 60 drops (4 ml) per minute The pressure of the perfusing system was readjusted from time to time to maintain this rate of perfusion for 30 minutes. The same amount of perfused blood was ex tracted each minute by phlebotomy Aortic and left atrial pressures were recorded continuously Every 15 minutes the per fusion was stopped for 30 seconds and the catheter was connected with the electro-manometer so that back pressures could be recorded The perfusion was then con tinued After 30 minutes of perfusion with unsaturated blood 20 ml of the same un saturated blood was rapidly perfused into the cannulated artery at a pressure o about 270 mm Hg the injection took abou 5 seconds. The artery was then not per fused for 5 minutes, following which 2 ml of the dog s own arterial (saturated blood was again rapidly perfused. Sinc there was no change in rate or rhythm and no changes in pressure occurred i the aorta a solution of 6 per cent dextra (American type) in normal saline (a

20°C) was perfused by the same tech nique at the same rate for 30 minutes. Similar records were obtained Phlebotomy was likewise performed In 3 dogs, during the 30 minutes of perfusion of dextran the respirator was stopped and the intra tracheal tube occluded for 1 m nute. After 30 minutes of perfusion of dextran 20 ml. of unsaturated blood was perfused and 5 minutes later 20 ml of normotonic saline solution was perfused At the end of 80 minutes of the different perfusions the dogs were killed by exsanguination from the femoral artery Perfusion of dextran into the coronary artery at the rate of 60 drops per minute was continued until exsanguination was complete

In 4 *control dogs* the anterior descending coronary artery was cannulated as before and unsaturated heparinized blood was perfused at a *low pressure* about 20 mm Hg to the distal part of the artery Just after the cannulation and during the per fusion extrasystoles appeared the fre quency of which stead ly increased Th minute backflow in the same coronary branch decreased to 0 (Fig 4 C) The left atrial pressure increased to 6 to 8 mm Hg and the aortic pressure decreased gradu ally to 40 to 60 mm Hg Ventricular fibril lation occurred in all animals during the first 17 minutes of perfusion. Institution of cardiac massage and defibrillation failed to restore the normal heartbeat. The perfusion pressure of the unsaturated blood was then increased to about 130 mm Hg After such a perfusion at systemic pres sure level for 3 minutes cardiac massage and repeated attempts to defibrillate re stored normal rhythm in only 1 dog F brillation was irrevers ble n the other 3

Th second subject to be in estigated is the functional changes of *hypert ophied hearts* after perfusion of the anterior de scending coronary artery with unsaturated blood or dextran by the same technique as before

In a second series of 5 mongrel dogs which weighed from 15 to 20 kilograms a *descendi g aort left at ial shunt* was pro duced w th a Dacron graft 6 mm. in diameter (F g 3) The techn qu has been lescribed pre iously [19] Preoperat vely an teroposterior chest x-ray films were made and the hematocrit and hemoglobin were estimated Blood volumes were determined by an isotope dilution method using radio-active-iodine-labelled serum albumin (I[131] HSA) Sixty days later roentgenographic evidence of enlargement of the heart was present. Determination of blood volumes showed an increase of 23 to 28 per cent in 4 dogs. The hematocrit and hemoglobin ratio were normal The left thorax was then reopened In all of the animals the left atrium was considerably dilated and a strong thrill was palpable. Atrial fibril lation was present in all animals, and all grafts were patent and strongly pulsatile

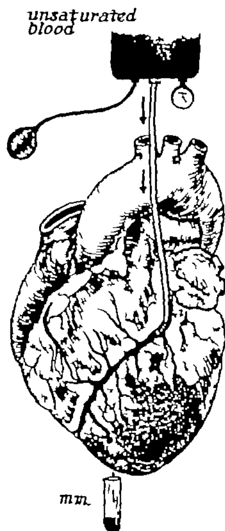


Fig 2 Unsaturated heparinized blood is perfused under pressure of bout 130 mm Hg into the distal part of the anterior descending coronary artery



Fig. 3. Descending aorta–left atrial shunt with Dacron graft.

The left atrium and descending aorta were cannulated and pressures were recorded continuously. The left atrial pressure was between 14.6 and 18.7 mm. Hg and the aortic pressure was between 120/60 and 130/60 mm. Hg. The branches of the left anterior descending coronary artery were of type A in 3 dogs and of type B in 2 dogs.[8] After heparinization of the animals as before the backflow in the fourth left branch of the anterior descending artery was measured. The minute backflow was between 0.05 and 0.15 ml. (average 0.10 ml.) (Fig. 4 *B*) and the oxygen content was 15 to 18 volumes per cent. The anterior descending coronary artery was then cannulated as before. During cannulation ventricular fibrillation occurred in 1 dog. *Institution of cardiac massage and defibrillation* restored the normal beat. After a repeated attempt at cannulation ventricular fibrillation occurred again and was this time irreversible. The back pressures in the cannulated anterior descending artery of the other 4 dogs ranged from 17/10 to 25/15 mm. Hg (average 21/12 mm. Hg) (Fig. 5 *B*). After occlusion of the anterior descending artery the back *flow decreased to 0, the aortic pressure* decreased to 100/50-110/50 mm. Hg, and the left atrial pressure increased still more to 20/8-22/10 mm. Hg. At this point extrasystoles appeared. Unsaturated hepar*inized blood was then perfused as before* into the distal part of the anterior descending artery over a period of 30 minutes. The same amount of perfused blood was extracted by phlebotomy. Aortic and *left atrial pressures were recorded con*tinuously. Back pressures in the coronary arteries were recorded every 15 minutes. After 30 minutes of perfusion with unsaturated blood the Dacron graft was clamped and the perfusion was continued for 15 minutes more. The clamp was then released and 20 ml. of the same unsaturated blood was rapidly perfused as before. Five minutes later 20 ml. of the dog's own arterial (saturated) blood was rapidly perfused. Since there was no change in the rate or rhythm and no changes in pressure occurred, a solution of 6 per cent dextran in normal saline was perfused for 30 minutes as before. The Dacron graft was then clamped again and the perfusion was continued for 15 minutes more. Phlebotomy was likewise performed. At the end of each experiment the dogs were killed by exsanguination via the femoral artery.

Results

All the dogs survived until the planned time of sacrifice with the exception of 1 *dog in the second group which died during* the cannulation. The first hemodynamic changes after occlusion of the anterior descending artery in both groups of animals have already been mentioned (Fig. 1).

Electrocardiogram in hypopituitarism
Reversibility of changes during treatment

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Electrocardiographic changes associated with hypopituitarism have been given little attention in textbooks of endocrinology and electrocardiography but the articles of some authors indicate that electrocardiographic abnormalities in cases of this disorder are of high incidence. Sheehan and Summers having studied electrocardiograms in 20 cases of pituitary insufficiency suggested that these changes were similar to those in myxedema. Whittaker reviewed electrocardiograms in 9 cases of hypopituitarism and found flattening of T waves and low voltage of QRS complexes. Querido in the electrocardiograms of 10 patients also observed ST-T abnormalities in 9 cases and low voltage in 3 cases.

Electrocardiographic patterns in hypopituitarism were reported by some authors to be similar to those in hypothyroidism whereas others found them similar to those of adrenal cortical hypofunction. The reversibility of electrocardiographic changes during treatment is not yet fully clarified. Bernart and Andino[4] did not find any alterations in electrocardiograms after oral administration of 0.5 to 1 grain of desiccated thyroid to patients with post partum hypopituitarism. Opposite results were reported by Beck and Montgomery,[6] who noted distinct electrocardiographic improvement in 3 patients on combined treatment with cortisone and doses of 2 to 3 grains of thyroid daily.

Our studies were performed in order to clarify whether electrocardiographic changes depend upon thyroid or adrenal cortical hypofunction. Moreover, our studies were intended to indicate whether electrocardiographic abnormalities are reversible during an adequate hormonal treatment of patients.

Material and methods

Twenty patients with typical hypopituitarism have been examined during the last 10 years. Of these, 11 were women and 9 were men whose ages ranged from 22 to 63 years. The cause of pituitary insufficiency varied but the majority of our patients had tumors arising from or damaging the pituitary gland. Six patients had chromophobe adenomas (verified at operation in 5 cases), 2 others had eosinophilic adenomas with long lasting manifestations of acromegaly. Hypopituitarism in 2 patients resulted from a craniopharyngioma—in one case from meningitis, in another from a malignant tumor of the optic tract and in still another from a cerebral hemorrhage in the region of optic chiasma. Three women had typical post-partum pituitary insufficiency (Sheehan's syndrome). Finally, 4 patients had hypopituitarism of unknown etiology.

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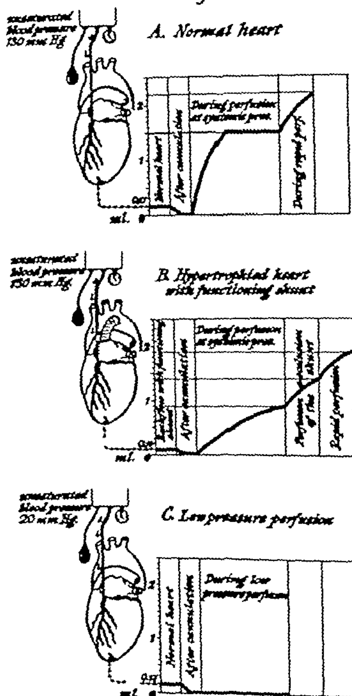
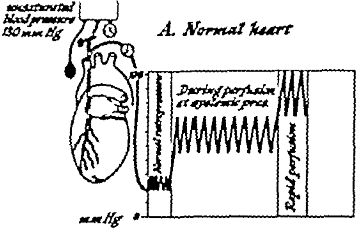


Fig. 4. *A*, Backflow during perfusion of unsaturated blood through the anterior descending coronary artery of normal hearts at systemic pressures and higher (1 0 mm. Hg). *B*, Backflow during perfusion of unsaturated blood through the anterior descending coronary artery of hypertrophied hearts at systemic pressures and higher (170 mm. Hg). *C*, Backflow during perfusion of unsaturated blood through the anterior descending coronary artery of normal hearts at low pressures (20 mm. Hg).

Back pressures



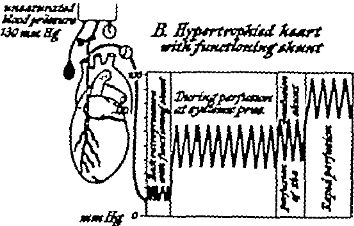


Fig 5 A Retropressures of the anterior descending coronary artery of normal hearts during perfusion of unsaturated blood through the artery at systemic pressures or higher (270 mm. Hg). B Retropressures of the anterior descending coronary artery of hypertrophied heart during perfusion of unsaturated blood through the artery at systemic pressures or higher (270 mm Hg)

Three to 5 minutes after the above-mentioned occlusion the anterior wall of the left ventricle became blue in color The upper limit of this change in color was well demarcated and extended from the level of the occlusion of the artery to the left border of the heart down to the apex of the heart and from the interventricular sulcus to the left border of the heart. Otherwise the color of the left ventricle was pink. The transition between blue and pink areas was very characteristic and remained unchanged during the whole time of several perfusions of unsaturated blood of dextran and even after abrupt perfusion of 20 ml. of saturated blood Two to 5 minutes after the beginning of the perfusion of unsaturated blood to the animals with normal and hypertrophied hearts the extrasystoles disappeared and the normal heartbeat was restored The left atrial pressure decreased and the aortic pressure increased to the preocclusion values (Fig 1) When during the perfusion the aortic-left atrial shunt was occluded the left atrial pressure decreased gradually to 9/3-16/7 mm Hg and the aortic pressure increased to 120/72 130/90 mm Hg Abrupt perfusion of 20 ml of saturated or unsaturated blood changed neither the rate of the heart nor the above-mentioned pressures nor did perfusion

of dextran for 30 minutes. Repeated rapid perfusion of 20 ml. of unsaturated and saturated blood, dextran, or normal saline after the 30 minutes of dextran perfusion produced no change. The average back pressure of the anterior descending arteries in the first series of dogs increased from an average 29 19 mm. Hg after occlusion of the artery to 0 45 mm. Hg during the several perfusions (Fig. 5,A). No difference in the values of back pressure was noted when unsaturated blood or dextran was perfused. Immediately after rapid perfusion with the above mentioned fluids the back pressure rose from 100 80 to 105 85 mm. Hg (Fig. 5,A). The back pressure in the dogs with a functioning shunt increased from an average 21 12 mm. Hg after occlusion of the artery to 65 35 mm. Hg during the several perfusions (Fig. 5,B). When the shunt was occluded the back pressure in the coronary artery increased gradually to 68 40 mm. Hg (Fig. 5,B). Immediately after rapid perfusion with the above mentioned fluids the back pressure rose from 90 65 to 102 75 mm. Hg (Fig. 5,B). The backflow in dogs with normal hearts increased from an average 0 17 ml. per minute before occlusion to 1.5 ml. per minute during perfusion (Fig. 4,A). When unsaturated blood was perfused, the oxygen content of the collected backflow blood was 8 to 9 volumes per cent and 3 to 5 volumes per cent when dextran was perfused. The backflow in the dogs with functioning shunt increased from an average 0 1 ml. per minute before occlusion of the coronary arteries to 0 9 ml. per minute during the perfusions (Fig. 4,B). When the Dacron graft was clamped the backflow gradually increased to 1 4 ml. per minute during perfusion (Fig. 4,B). When unsaturated blood was perfused the oxygen content of the collected backflow blood was 7 to 9 volumes per cent and it was 3 to 5 volumes per cent when dextran was perfused. The oxygen content did not change after occlusion of the shunt. Anoxia after occlusion of the intratracheal tube for 60 seconds increased the left atrial pressure 2 to 4 mm. and decreased the systemic pressure 10 to 30 mm. One minute after restoration of the cyclic insufflation of the lungs the pressures returned to the previous normal.

During exsanguination of the heart by a free flow of blood from the femoral artery while dextran was being continuously perfused, the normal heartbeat continued, the arterial pressure decreased gradually, and when an amount of blood equal to 6 to 7 per cent of the body weight had been removed the heart stopped in diastole.

Heart weights were obtained in the dogs with aortic left atrial shunts after complete excision of the tissues adherent to the heart and transection of the great vessels to their bases. The calculated predicted ratio of heart weight to body weight on the basis of the formula of Herrmann[18] showed evidence of hypertrophy of the heart of from 31 to 40 per cent in all animals.

Discussion

It is generally observed that the occlusion of the left anterior descending coronary artery increases the left atrial pressure and decreases the systemic pressure while the right atrial pressure remains unchanged.[21] Disorders of rhythm, diminished output, and cyanosis of the left ventricle follow. In our experiments, after occlusion of the anterior descending coronary artery the above-mentioned phenomena were present within 1 to 3 minutes. After about 2 minutes of perfusion of the artery with venous blood at systemic pressures the left atrial pressure and systemic pressures returned to previous levels and normal cardiac rhythm returned. Even animals with hypertrophied hearts and an increased left atrial pressure after an aortic-left atrial shunt could tolerate these perfusions. However, the myocardium remained cyanotic over the area of distribution of the artery. Heartbeat and pressures remained stable during 30 minutes of perfusion with unsaturated blood and during the following 30 minutes of perfusion with dextran. Rapid perfusion of 20 ml. of unsaturated blood, saturated blood, or dextran did not alter the heartbeat or pressures. The backflow in a branch of the artery was increased 5 to 8 times more than the normal during the perfusion and the oxygen content was decreased, especially when dextran was perfused. In the group of animals with aortic left atrial shunt when the shunt was occluded

during the coronary perfusions the left atrial pressure decreased and the aortic pressure increased more than the preperfusion levels when the shunt was functioning. It is noteworthy that the reduction in oxygen saturation of the cyanotic area of the myocardium especially during perfusion with dextran and of the surrounding red myocardium did not produce electrical instability and fibrillation during the 90 to 100 minutes of perfusion in any of our 14 experiments even in animals with hypertrophied hearts.

In the literature we were able to find several instances of differences in oxygen tension within the myocardium which did not necessarily produce a break in the coordinate mechanism of the heartbeat. For example ligation of the coronary sinus or of the great cardiac vein produced high venous pressure which was sometimes equal to systolic aortic pressure.[33,34] The reversal of flow in the coronary sinus extends to the arteries resulting in a considerable decrease in coronary artery inflow. The backflow of blood from the anterior descending coronary artery can be increased after the occlusion of the sinus from the normal level of 1 ml. per minute to a level as high as 39 ml. per minute.[33] This blood is highly unsaturated and contains only 3 to 4 volumes per cent of oxygen whereas the highest oxygen content of the coronary sinus was approximately 8 volumes per cent. These *findings lead* us to conclude that great differences in oxygen content of the right and left ventricular myocardium do not produce ventricular fibrillation. The resulting low regional saturation and decreased oxygen content of the vascular bed of a circumscribed area of the left ventricle after perfusion of an artery with unsaturated blood or dextran can be compared with the effect of ligation of a major vein. The only difference in the two instances is that after ligation of the vein the coronary venous pressure is high. In both instances the great difference in oxygen content which occurs in two circumscribed areas of the ventricular myocardium does not produce ventricular fibrillation.

After coronary artery perfusion with venous blood or dextran or even after coronary sinus obstruction a high pressure of unsaturated blood was supplied to the coronary vascular bed which was able to support normal myocardial action. When the pressure of the inflow of unsaturated blood to the coronary arteries was low fibrillation occurred. It has been shown that animals previously "protected" by cardiopulmonopexy can subsequently be subjected to ligation of the coronary artery without mortality because the low pressure saturated pulmonary blood which reaches the myocardium through the vascular bed of the newly formed adhesions effectively supplies the ischemic *myocardium*.[3,7] The results of the reversal of the protective action of cardiopulmonopexy to the ischemic myocardium suggest the inability of low pressure unsaturated blood to maintain normal ventricular contraction. When for example the homolateral bronchus was occluded in these animals ventricular fibrillation occurred after some minutes.[7] This experiment indicates that *low-pressure arterial blood* can effectively supply the ischemic myocardium after coronary occlusion. Conversely *inflow of venous blood under low pressure* cannot maintain normal contraction of the ischemic myocardium.

Furthermore determination of the volume of blood in the ischemic myocardium during a 30-minutes period after coronary ligations shows a decrease to two thirds of normal in the subendocardial layer whereas in the subepicardial portion the volume of blood in the ischemic myocardium was equal to that in the adjacent nonischemic area.[35] These observations confirm that the volume of blood contained in a particular portion of the ischemic myocardium at the time of its determination is not responsible for ventricular fibrillation but rather the rate of blood flow and pressure. Deaths which follow upon acute coronary insufficiency without acute coronary occlusion[13] show that regional myocardial hypoxia may be fatal when coronary artery inflow is suddenly decreased. The increase in coronary artery inflow and pressure with venous blood or even dextran in our experiments restored and maintained the normal myocardial contraction.

It is generally agreed that the coronary arteries are end arteries in a physiologic sense.[34] Freely communicating anastomoses rarely appear after coronary occlusion until 2 weeks have elapsed. Perfusion of unsaturated blood or dextran under pressure opens these intercoronary anastomoses immediately. This is indicated from the fact that the backflow in a divided branch of the perfused anterior descending coronary artery was very much greater than the backflow when the artery was not occluded and supplied with arterial blood.

Flow through the left anterior descending coronary artery in the normal resting dog averages about 1.17 ml. of blood per minute per gram weight of left ventricular muscle. Flow through the anterior descending coronary artery of a 15-kilogram dog, for example, will be about 23 to 30 ml. per minute. It was surprising that only 4 ml. of unsaturated blood or dextran perfused each minute at systemic pressures to the anterior descending coronary artery could maintain the normal heart beat not only of normal but even of hypertrophied hearts. The unexpected uncomplicated heart function after 30 minutes of coronary perfusion with dextran could perhaps be due to a decrease in the viscosity of the stagnating blood in the ischemic region of the myocardium with a resulting decrease in the intravascular aggregation of the red cells, platelets, and chylomicrons.[8-] In this way the impaired capillary flow of the anoxic region of the myocardium could be increased by creating conditions which would allow the immediate opening of the intercoronary anastomoses.

The observation that fibrillation may occur within 20 seconds after sudden release of a temporarily occluded coronary artery[28] is not contrary to our experiment. The abrupt increase in the coronary pressure after release of the occlusion occurring in a condition of low retropressure (average 29.19 mm. Hg) of the occluded artery can produce fibrillation. On the other hand, abrupt increase in the coronary arterial pressure in a condition of high retropressure (0.50 mm. Hg) of the perfused artery is well tolerated. Abrupt perfusion within 5 seconds, of 20 ml. of unsaturated blood, saturated blood, or dextran to the previously perfused coronary artery of 10 dogs produced neither fibrillation nor any change in heart rhythm.

From the foregoing, we can conclude that a decrease in oxygen content of the myocardium does not produce fibrillation when unsaturated blood or dextran is perfused under *high pressure* to a coronary artery, the branches of which are distributed to the anoxic region. When unsaturated blood at *low pressure* is perfused fibrillation ensues.

It is premature to state that the direct perfusions of the coronary arteries with saturated or unsaturated blood can be applied as surgical treatment of acute coronary occlusion or acute postoperative heart failure. The clinical significance of coronary perfusion in the presence of acute heart failure will be the subject of future study.

Summary

1. Perfusion of unsaturated blood or dextran at systemic pressures for 30 minutes into the anterior descending coronary artery of normal and hypertrophied hearts did not alter the rate of heartbeat nor the aortic or left atrial pressures. Perfusion of unsaturated blood at low pressures does result in fibrillation.

2. Rapid perfusion of 20 ml. of unsaturated blood, saturated blood, or dextran during or after the above mentioned perfusions did not alter heartbeat or pressures.

3. The retropressure and backflow increased during these perfusions.

4. Obstruction of the intratracheal tube for 60 seconds during the perfusion was well tolerated.

5. Gradual exsanguination of the animals during perfusion of dextran permitted total exsanguination without the appearance of fibrillation.

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The effects of respiration on aortic pressure and flow

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In normal human subjects, inspiration lowers the systolic blood pressure 3 to 10 mm. Hg, and a somewhat greater decline is found in anesthetized dogs. A much larger inspiratory fall in blood pressure occurs in restrictive pericardial disease and with respiratory obstruction. Review of the literature does not uncover the mechanism for either normal or abnormal respiratory fluctuation in blood pressure. One reason for the confusion in regard to the causes of normal and abnormal inspiratory decline in blood pressure is that the effect of inspiration on simultaneously recorded aortic pressure and flow has not been reported. This paper compares the effects of inspiration on pressure and flow in the aorta of the anesthetized dog under control conditions and under circumstances known to exaggerate fluctuations in arterial pressure, namely, acute cardiac tamponade, acute airway obstruction, and vagotomy.

Some explanations for inspiratory decrease in aortic pressure imply a simultaneous decline in aortic flow, whereas others do not. In normal human subjects and in patients with labored breathing[4] the fall in pressure has been ascribed to transmission into the aorta of the inspiratory decline in intrathoracic pressure. This explanation does not require inspiratory fall in aortic flow. Reflex lowering of peripheral vascular resistance has been reported when the dog's lung is stretched mechanically. Such a reflex could increase aortic flow or decrease aortic pressure. The other hypotheses require that an inspiratory fall in aortic flow accompany an inspiratory fall in pressure. Inspiratory pooling of blood in the lungs[4] or right heart has been considered to lead to reduced left ventricular ejection in normal subjects and in patients with restrictive pericardial disease. The pericardium is thought to restrict the size of the heart.[11] Inspiratory traction on the pericardium by mediastinal structures may further limit left ventricular volume and so produce a small inspiratory decrease in aortic flow and pressure in normal subjects and profound inspiratory decline in aortic flow and pressure in some pericardial disorders. The normal inspiratory fall in aortic pressure may reflect diminished aortic flow caused by diminished right

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Fig. 1. Arrangement to divert left ventricular output to descending aorta and maintain cerebral flow.

heart output *during the preceding expiration*. In restrictive pericardial disease atrial pressure has been said to fall less during inspiration than vena caval or pulmonary venous pressures causing decreased filling of both atria and consequently decreased ejection from both ventricles.

Simultaneous measurement of aortic pressure and flow in inspiration and expiration and their relationship to respiratory variations *in pulmonary arterial* pressure would provide useful data in regard to normal and abnormal inspiratory decline in aortic pressure, and would help differentiate the effects of inspiration on the two ventricles.

Methods

Mongrel dogs were anesthetized with pentobarbital (26 mg. per kilogram). The chest was opened during the administration of oxygen under intermittent positive pressure. Two polyethylene catheters were sutured in watertight fashion in the pericardial sac. The necessity to preserve the pericardium intact and leakproof made it impossible to place a flow transducer on *the aortic root*. *Aortic stroke flow* was measured therefore with an electromagnetic flowmeter probe placed around the origin of the descending aorta after an anastomosis had been constructed to maintain cerebral flow and yet divert the left ventricular stroke volume (minus coronary arterial flow) to a location at which it would be sensed by the transducer (Fig. 1). To accomplish this the left subclavian artery was ligated at its origin, a thin-walled wide-bore plastic tube shunted blood from a femoral artery to a carotid artery, *and the brachiocephalic artery* was ligated at its origin. The circumference of the aorta just below the origin of its left subclavian branch was *measured*. A magnetic probe selected to fit snugly but with minimal compression was placed around the measured segment of aorta. A No. 8 Cournand catheter was placed so that its tip lay in the descending aorta 1 cm. below the magnetic probe. In three instances, additional plastic catheters were placed in segmental branches of the left pulmonary artery and vein. The chest was closed and the tip of a Wiggers pleural *cannula was left in the pleural space*. The dog was disconnected from the respirator and resumed spontaneous respiration. The dogs were studied under general anesthesia a few hours after thoracotomy and it was necessary to leave a small volume of liquid in the chest to dissipate the heat generated in the electromagnet. Pericardial, pleural, and pulmonary venous pressures were measured by Statham P23Bb gauges, and systemic and pulmonary arterial pressures *were measured* by *Statham* P23Db gauges. Pressures were registered by Sanborn preamplifiers on a Sanborn multichannel recorder. Aortic flow was measured with a Carolina Electronics square wave electromagnetic flowmeter* and recorded by a Sanborn D.C. coupling preamplifier on the Sanborn recorder. The position of the zero flow line was established by injecting acetylcholine into the jugular vein in sufficient amount to cause asystole of several seconds duration. The flowmeter was calibrated in situ at the end of each experi

*Carolina Medical Electronics, Inc., Winston-Salem, N. C.

ment. To accomplish this the dog was killed and the chest was reopened without disturbing the exact position of the flow meter probe about the aorta. A large cannula was inserted into the aorta just below the probe, and a known volume of the same dog's blood previously collected for the purpose was injected past the probe. The polarity of the flowmeter was electrically reversed to obtain an upright signal and at least three calibration curves were recorded

Physiologic saline was infused into the pericardial sac until the intrapericardial pressure rose 3 to 15 mm Hg above control value. At higher intrapericardial pressures the blood pressure was so low that variations in pressure and flow were not well developed. In most instances, studies during tamponade were made with intrapericardial pressures approximately 10 mm Hg above the control levels.

After the animal had recovered from acute cardiac tamponade the endotracheal tube was partially occluded so that respiration was labored In other experiments the pattern of respiration was altered by bilateral vagotomy

In 3 additional dogs a different experiment was performed. The content of the left subclavian artery was drained into a dependent reservoir and was pumped at a constant rate into the descending aorta via a femoral artery The descending aorta was ligated immediately below the origin of the left subclavian artery The pericardium was cannulated and the chest was closed After the resumption of spontaneous respiration blood pressure was measured in the ascending aorta, which was perfused by the left ventricle, and in the descending aorta, which was perfused by the pump (Fig 2)

Results

In the first experiment satisfactory data were obtained from 9 dogs, in each of which several records were obtained during the control experimental and recovery periods.

Control Each dog manifested inspiratory decrease in both aortic pressure and flow (Fig 3) and during inspiration the systolic pressure declined 3 to 24 mm. Hg depending upon the depth of respiration. Aortic stroke flow peak velocity and pulse pressure also declined although the systolic pressure varied more than the diastolic. Aortic stroke flow and pressure were minimal at the nadir of inspiration and maximal as soon as the intrapleural pressure resumed its expiratory level Pressure and flow declined slowly when little further change in intrapleural pressure was taking place and more rapidly as inspiration was inscribed. Yet pulmonary arterial pressure changed very little until inspiration when it rose steeply to its maximum at the nadir of inspiration at which time the aortic pressure and flow were minimal (Fig 3) When the intrapleural pressure ascended rapidly from nadir to expiratory level the maximal aortic pressure and flow occurred one beat after the maximal pulmonary arterial pressure. When this ascent was more gradual, there were two or three beats between maximal pulmonary arterial pressure and maximal aortic pressure and flow

Tamponade Cardiac tamponade greatly exaggerated the inspiratory fall in aortic pressure and stroke flow but the relationships between aortic intrapleural, and pulmonary arterial events were exactly the same as in the controls (Fig 3) In each dog cardiac output was decreased in proportion to the severity of cardiac com

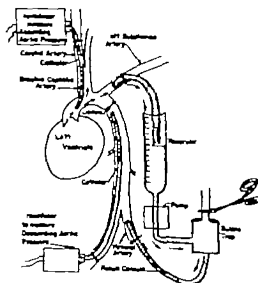


Fig 2. Arrangement to perfuse the ascending aorta from the left ventricle and the descending aorta at constant rate with pump.

PULMONARY ARTERY
mm Hg
AORTA
mm Hg
PERICARDIUM
mm Hg
PLEURA
mm Hg
FLOW IN DESCENDING AORTA
cc/min
Paper Speed 25 mm/sec.

CONTROL

TAMPONADE

Fig 3 The effect of cut lev tion of intr pericardial pressure on the respir tory ariations of aort nd pulmonary arterial pressure nd ar tic stroke flow In the ontrol aortic systolic pressure declines 20 mm Hg with inspiration Aortic diastolic pressure declines 5 mm. Hg Aortic strok flow declines 4.6 cc or 28 per cent of maximal flow N t pulmonary terial pressure is le ted duri g in pir tion During ardiac tamponade pericardial pressure is lev t d by 8 mm Hg Not the inspir tory fall in aortic systolic tolic pressure of 43 m Hg in aort dia olic pres re of 25 mm Hg nd in aortic t oke flow of more tha 12 cc or 98 per cent of maximal flow N t pulmonary rterial pressure rose 1 i g inspir tion

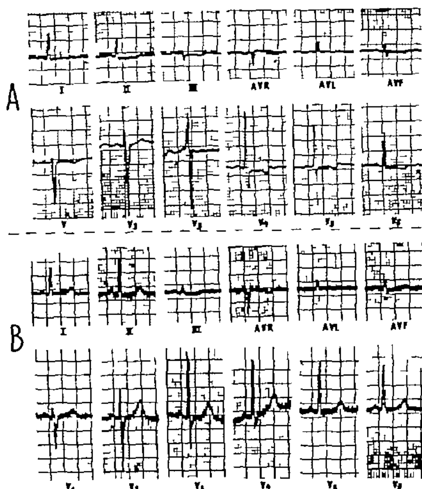


Fig. 1. Case 1. J. Z. 32 year-old woman with post partum pituitary insufficiency. A. Before treatment the electrocardiogram shows inverted T waves in Lead I, II, V, V, V, V and depressed S-T segment in Lead V and V. B. After 10 days of treatment with cortisone the electrocardiogram reverted to normal, the T waves became positive and the S-T segments returned to the isoelectric line.

Roentgen examination showed a normal cardiac silhouette in 16 patients. In 2 patients the heart was small as in Addison's disease and in 2 other patients it was slightly enlarged but with no signs of pericardial effusion.

Clear clinical and laboratory evidence of gonadal and adrenal cortical hypofunction was found in all patients, in most of them signs of secondary hypothyroidism were also seen. The 17-ketosteroid excretion in urine was very low: 4 to 0 mg. per 24 hours. Similarly, the urinary 17-hydroxycorticoid excretion (method of Reddy and associates) was decreased and ranged from 0.1 to 1.0 mg. per 24 hours. In female patients the vaginal smears showed atrophic changes. The water loading test showed a strikingly impaired diuresis; a substantial improvement in diuretic response occurred during treatment with cortisone. After water loading overhydration of the red blood cells was found in all patients.

The basal metabolic rate was normal in 3 patients only. In the other 17 patients it was in the hypothyroid range: −18 to −40 per cent. In 3 patients the levels of serum cholesterol were above the normal range: 310 to 460 mg. per 100 ml. In addition, in 10 patients the serum cholesterol was at the upper limit of the normal values: 250 to 300 mg. per 100 ml. The uptake of radioactive iodine, tested in 15 patients,

pression In a dog in which there was fairly severe compression the cardiac output was decreased from over 1,800 ml per minute to 550 ml per minute. In the control aortic stroke flow varied from 10 1 ml for inspiration to 12.0 ml. for expiration. During cardiac tamponade sufficient to raise the intrapericardial pressure by 10 mm Hg the respiratory variation in aortic flow increased and was 1 6 ml. for inspiration and 7 9 ml. for expiration

In the control animals reversed flow occurred at the end of each aortic flow pulse With tamponade this reversed flow was often absent or greatly reduced (Fig 4) depending upon the severity of compression of the heart and first part of the ascending aorta.

Acute airway obstruction Acute obstruction to the airway resulted in labored breathing large fluctuations in intrapleural pressure and respiratory variations in aortic pressure as great as those recorded during cardiac tamponade The fall in pressure differed from that seen with cardiac tamponade. With inspiration aortic systolic and diastolic pressures fell equally and no decrease in pulse pressure resulted In this situation respiratory variation in calculated stroke flow was not increased Fig 4 illustrates pronounced respiratory variation in aortic pressure but little change in peak velocity of aortic flow Aortic pressure and calculated stroke flow were increased rather than decreased as they had been during cardiac tamponade

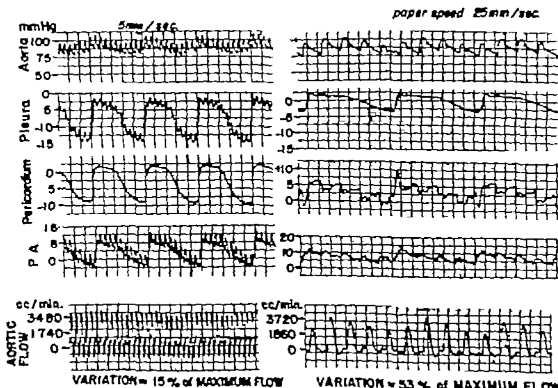


Fig 4 With partial airway obstruction (*left*) the intrapleural pressure fluctuates 15 mm. Hg intrapericardial pressure fluctuates 12 mm. Hg and pulmonary arterial pressure fluctuates 10 mm. Hg Fluctuations in aortic systolic and diastolic pressures of 14 mm. Hg are associated with 15 per cent variation in stroke flow (computed from the t preceding respiratory cycles recorded at high paper speed and not shown). Compare with tamponade (*right*) in which decline in aortic systolic pressure of 12 mm Hg in inspiration is accompanied by respiratory fall in aortic stroke flow that amounts to 53 per cent of maximal flow (stroke flows computed from cardiac cycles illustrated in the figure).

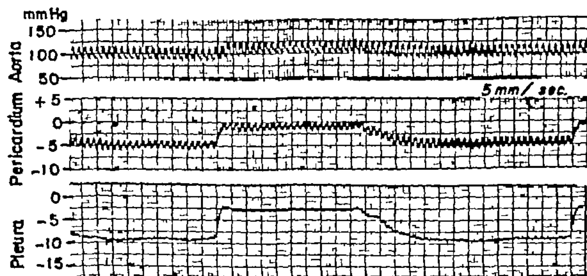


Fig 5 After vagotomy the intrapleural pressure rises slowly from inspiratory to expiratory level. Aortic pressure likewise rises slowly. Six beats occur between minimal and maximal aortic pressures.

Bilateral vagotomy increased the depth and duration of inspiration and lowered the respiratory rate (Fig 5) The resulting increased variation in aortic pressure like that associated with obstruction to the airway and unlike that associated with cardiac tamponade was not accompanied by large respiratory variations in aortic stroke flow Although the heart rate was rapid and the respiratory rate was slow aortic pressure began to decline at the onset of inspiration.

Variations in aortic pressure during constant aortic flow In 3 dogs the descending aorta was perfused at constant rate by a pump The ascending aorta was perfused simultaneously by the left ventricle In spiration lowered the pressure in the ascending aorta. There was a lesser inspiratory fall in descending aortic pressure which was comparable in magnitude to the inspiratory fall in intrapleural pressure (Fig 6)

Discussion

Limitations of the experimental design. Because it was essential to maintain the pericardium leakproof the large probes of our square wave electromagnetic flowmeter could not be placed at the roots of the aorta and pulmonary artery to record systemic and pulmonary flow simultaneously Gux and his associates[22] were able to place the considerably smaller coreless probes of their electromagnetic flowmeter at these sites and to close the pericardium. Their paper does not state whether the pericardium was sutured in a water tight manner The flow section of the pulsed ultrasonic flowmeter[23] can be placed with crystals on the aortic and pulmonary roots, and the pericardium probably could be completely closed Inaccessibility of the roots of the great vessels necessitated resort to ligation of the aortic arch branches at their origins, and anastomosis between a femoral and a carotid artery in order to place the transducer where it would sense the total output of the left ventricle except the coronary flow

Our data were recorded from intact dogs under general anesthesia Franklin and associates[23] found that respiratory variations in right ventricular output preceded variations in left ventricular output by one cardiac cycle in healthy dogs, but by several cardiac cycles in dogs with hydrothorax or pulmonary atelectasis. They concluded that recent thoracotomy and anesthesia caused atelectasis and labored breathing and that the resulting high resistance interposed between the ventricles was the cause of exaggerated respiratory variations that were grossly out of phase. But the phase relationships of the aortic and pulmonary arterial pres-

sures in our dogs, and their relationship to events in the respiratory cycle were the same as those we have observed in patients during combined heart catheterization. Furthermore Lauson and associates, studying unanesthetized patients found that inspiration increased pulmonary arterial pressures and lowered aortic pressures and in an earlier publication[24] we stated that in the dog the variations in aortic and pulmonary arterial pressure are almost 180 degrees out of phase.

Our present data explain these apparent discrepancies in the literature. Anesthesia influences the relationship between pulmonary arterial and aortic pressure by altering the mechanics of respiration and not by causing an obstruction between the ventricles. If anesthesia results in dyspnea, and the slope of expiration is prolonged maximal pulmonary arterial and minimal aortic pressures coincide normally but precede maximal aortic pressure by two or three beats. In dogs not affected in this way the slope of expiration is steep maximal pulmonary arterial and minimal aortic pressure again coincide but precede maximal aortic pressure by only a single beat. Furthermore, pulmonary stenosis causes a severe obstruction between the ventricles and yet the phase relation between pulmonary arterial and aortic pressure tracings in our catheterized patients with pulmonary stenosis does not differ from that observed in patients with other disorders. It is concluded that general anesthesia, recent thoracotomy a small pleural effusion and diversion of total left ventricular output to the descending aorta did not invalidate the results in our dogs.

Interpretation of results The present study confirms that normal inspiration lowers aortic pressure and demonstrates that this decline is accompanied by di

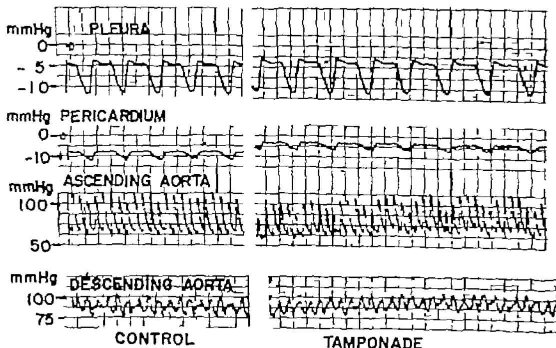


Fig. 4 *Control*. The descending aorta is perfused t a constant rate by pump. The *ascending* orta is perfused by the left ventricle. Inspiratory decline in pressure in the descending aorta is equivalent to the inspira ory fall in intrapleural pressure (8 mm. Hg) and is less than that in the ascending aorta (12 mm. Hg). *Tamponade* Inspiratory decline in pressure in the ascending aorta is increased to 22 mm. Hg. The corresponding fall in descending aortic pressure remains close to that in the pleura (9 mm. Hg).

minished aortic flow. Both phenomena are greatly exaggerated by cardiac tamponade. In control animals diminished aortic flow was found during inspiration, thus demonstrating that diminished aortic pressure was not caused solely by transmission of negative intrathoracic pressures to the aorta. This was confirmed by studies in which the content of the left subclavian artery was pumped at constant rate into a femoral artery and the descending aorta was ligated below the left subclavian artery. After the chest had been closed blood pressure during inspiration fell considerably more in the ascending aorta which was perfused by the left ventricle than it did in the descending aorta which was perfused by the pump. The conclusion was that only a portion of the normal decrease in aortic pressure during inspiration could be explained by transmission of increased negative intrathoracic pressure to the aorta. This result also showed that under the conditions of the experiment reflex peripheral vascular dilation did not accompany inspiration in sufficient degree to explain the decrease in aortic pressure.

Our measurements of aortic stroke flow during acute cardiac tamponade were not designed to explain the mechanism of pulsus paradoxus, nor do they do so. However, they offer direct proof that the profound inspiratory drop in aortic pressure (pulsus paradoxus) associated with acute cardiac tamponade was accompanied by large and abnormal respiratory variations in aortic stroke flow.

The observation of peak pulmonary arterial pressures at the trough of inspiration during tamponade and in the control suggested but did not prove that the normal inspiratory increase in right heart filling[4,24,27] was not abolished by cardiac tamponade. This observation is in accord with others from this laboratory. Shabetai and Fowler[23] measured phasic flow in the superior and inferior venae cavae in cardiac tamponade and found that flow in both of these vessels was increased during inspiration not only in the control but also during acute cardiac tamponade. It was concluded in those studies that the pulsus paradoxus which resulted from acute cardiac tamponade was not caused by decreased venous return during inspiration.

The inspiratory fall in aortic pressure that accompanies labored respiration whether produced by partial tracheal obstruction or by vagotomy may be as pronounced as that associated with cardiac tamponade but was not accompanied by grossly abnormal respiratory variations in aortic stroke flow. This observation confirmed that under these circumstances, it was caused by transmission to the circulatory system of the markedly increased fluctuations in intrathoracic pressures.[4,5] Bilateral vagotomy caused an exceedingly slow respiratory rate and tachycardia. The fall in aortic pressure coincident with the onset of inspiration could not have been a reflection of a respiratory variation in pulmonary arterial flow delayed by its transit time in the lungs. Had this been the case the decline should have occurred at the most three or four beats after expiration.

The diminution of the reversed flow at the termination of each aortic flow pulse during tamponade may be looked upon as teleologically advantageous. It is probably caused by the tense pericardial effusion tamponading the elastic first part of the aorta, thereby preventing its early systolic expansion and late systolic and diastolic recoil. An alternative explanation that aortic recoil is diminished because of the reduced stroke volume that occurs during tamponade is less likely in view of Spencer's observation[11] that in an individual dog backflow volume remains constant over wide ranges of forward stroke volume and arterial pressure.

Summary and conclusions

The mechanism of respiratory variation in aortic pressure was studied in anesthetized dogs.

In control animals, two factors contributed to this variation: an inspiratory decrease in left ventricular stroke output and transmission of the inspiratory fall in intrathoracic pressure into the aorta.

During cardiac tamponade the increase in the inspiratory decline of aortic pressure (pulsus paradoxus) was caused by a greater inspiratory fall in left ventricular stroke output and not by a decrease in peripheral arterial resistance or greater decline in intrathoracic pressure.

During tracheal obstruction the exaggerated inspiratory decline in aortic pressure was caused by increased fluctuations in intrathoracic pressure and not by greater inspiratory fall in left ventricular stroke output

The phase relationship between aortic and pulmonary arterial pressures was related to the slope of the intrapleural pressure as it climbed from the bottom of inspiration to its expiratory value

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Case reports

The diagnosis of aorticopulmonary septal defect

A case report with successful surgical closure

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Aorticopulmonary septal defect,[*] which has also been less appropriately termed *aortic pulmonary window, partial truncus arteriosus, aortic septal defect,* and *aortic pulmonary fistula*[1] is a relatively rare congenital anomaly that arises from defective partition of the primitive truncus arteriosus. Complete failure of growth of the elevated longitudinal ridges which arise on opposite sides of the common pulmonary artery–aortic trunk results in a persistent truncus arteriosus. A partial defect in the development and fusion of the ridges causes an aorticopulmonary septal defect (APSD). The defects vary widely in size (4 to 50 mm.) and occur between the ascending aorta and the main pulmonary artery 1.5 cm. or less above the aortic and pulmonic valves.[4] The semilunar valves themselves are normal.[*]

An aorticopulmonary septal defect is often erroneously diagnosed as a patent ductus arteriosus (PDA). This mistaken interpretation leads to an operation which is often unsuccessful. In the case to be reported the correct diagnosis was suspected after right ventricular angiography and was confirmed by retrograde aortography. A surgical procedure that utilized cardiopulmonary bypass resulted in successful closure of the defect.

Case report

A 34-year-old white male entered Barnes Hospital for the first time on April 20, 1953, at the age of 28 years. The patient had been noted to have a heart murmur at birth and had been restricted from sport. Nevertheless, he did well, noting only mild dyspnea on exertion and easy fatigue. During the previous year he developed increasing dyspnea and fatigue, intermittent cyanosis with exertion, and several episodes of mild hemoptysis. Bronchoscopy performed elsewhere was negative, and the patient was referred with a diagnosis of mitral stenosis.

The positive physical findings were limited to the heart and thorax. A slight left precordial bulge was noted. No thrill was palpable. The second sound in the pulmonic area was strikingly increased. A faint diastolic murmur was heard in the pulmonic area and along the left sternal border, and one observer described a faint mitral diastolic rumbling murmur. The initial clinical impression was rheumatic heart disease with mitral stenosis.

The hemoglobin was 17.1 Gm., but other routine laboratory studies were within normal limits. The electrocardiogram revealed left ventricular en-

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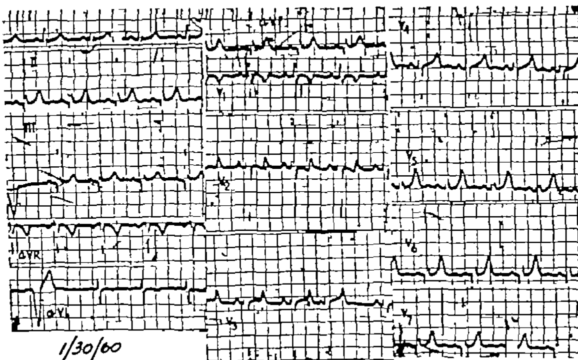


Fig. 1. Electrocardiogram taken on Jan. 30, 1960. The changes were considered to be compatible with biventricular hypertrophy. Occasional ventricular premature contractions are present.

largement on the basis of high voltage alone. The chest roentgenogram demonstrated left and right ventricular enlargement, (?) pulmonary artery segment, and an increase in size of the pulmonary vasculature. Cardiac catheterization was performed by Dr. Bernard Berenson in order to evaluate the possibility of congenital heart disease. The results (see Table I) were interpreted as indicating pulmonary hypertension due to high ventricular septal defect or defect at the level of the pulmonary artery. A retrograde aortogram was attempted via the right brachial artery with injection of 10 c.c. of 70 per cent Urokon into the right subclavian artery. Unfortunately, the aorta was not visualized. The final diagnosis at the time of the patient discharge was interventricular septal defect.

The patient was rehospitalized because of hemoptysis on Oct. 28, 1954, with the same complaints and findings. At this time the hemoglobin was 14.2 Gm., arm-to-tongue circulation time with Decholin was 10 seconds, and venous pressure was 103 mm. of saline. The right femoral arterial oxygen saturation at rest was 96.6 per cent. Several studies of the sputum for acid-fast bacilli were negative.

After the patient was discharged in November 1954 he developed substernal squeezing nonradiating chest pain which was precipitated by exertion or excitement and which subsided within 1 hour. The pain slowly became worse over several years. Several months before admission to the hospital he noted an increase in dyspnea on exertion, fatigue, and exertional cyanosis. Limitation of activity became severe. For these reasons the patient was admitted to Barnes Hospital for the third time on Jan. 29, 1960. At no time had he experienced ankle edema, orthopnea, paroxysmal nocturnal dyspnea, unusual susceptibility to respiratory infections, or acute rheumatic fever.

The blood pressure was 130/90 mm. Hg, pulse 84, respiration 20, and temperature 37°C. Clubbing and cyanosis were absent. The only positive findings

Table I. Catheterization studies

	1953		1960	
Chamber	Oxygen saturation (%)	Pressure (mm. Hg)	Oxygen saturation (%)	Pressure (mm. Hg)
SVC	61	—	51	—
IVC	—	—	56	—
RA	60	6/1	56	6
Low RV	60		53	
High RV	67	120/0	57	120/7
PA	79	120/60	76	120/72
RFA			97.3	
RBA rest			98.2	
RBA exercise			97.0	

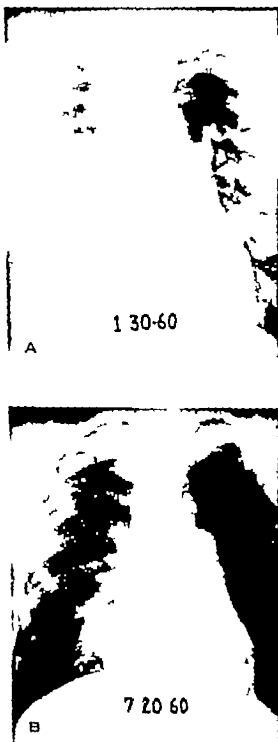


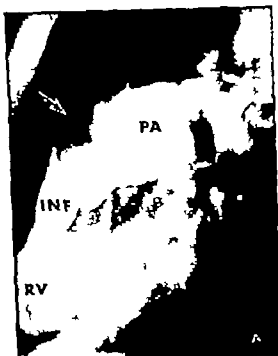
Fig. 2. *A*. Chest film taken on J 30 1960 Bi entricular and left atrial enlargement were noted. The central pulmonary rteries were d'lated but the vessels tapered rapidly in the peripheral lung fields. *B* Chest film taken July 20 1960 I comparison with the previous film the pulmonary vascularity ha decreased nd there ha been a minimal reduction in heart size.

were elicited on cardia examination There w left precordial prominence a loud pulmonic second sound with a fixed plit soft sy tolic ejection mur m long the left sternal border nd a f int early diastolic blowing murmur that w heard t the lower left ternal border The electrocardiogram w consistent w th bi entricular hypertrophy (Fig 1). Left trial nlargement bi ent icular enlargeme t and centr l pulmonary scula engorgement with rapid tapering in the outer one third of the lung fields were seen on chest roentgenogram (Fig 2,A). The hemoglo! was 16.8 Gm. Other rout ne laborat ry test were negative Femoral nd brachial arterial oxygen saturations (T ble 1) were normal before nd after xercise Catheteriz t n of the ight side of the heart gain rev led triking pulmonary h pertension with the incre se in oxygen sat ration occurring in the pulmonary rtery (T ble I) I order t define the natomy of the lesion further selecti angiocardiography wa performed using 48 c of 50 per cent Hypaque th the tip of the N 10 N I H ngiocardiographic theter the right ent icle This sit of injection w chosen so that entricular septal defect ould be excluded The radi paque d w injected in l second nder pressure of 5 kg per centimeter using Cadbond) utomatic i jector The tud demonst ted that there was no right to-left sh nt cross the entricul sept m. The pulmonic valves ere thickened but not tenotic The peripheral pulmonar teries were markedly narrowed The most triking find'ngs were marked dilatation of the main pulmonary artery nd dilution ffect few entimeters above the pulmonic al e (ar teriorly and t the right (Fig 3,A and B). The unusual loc tion of the dilution effect suggested the presence of AMSD or PDA w th atypic l opening

I ew of the angiographic findings it w neces sary t perform aortogr phy A No. 10 N I H atheter w introduced through the exposed right femoral rtery nd passed into the ascending aorta Forty fi e cubic centimeter of 50 per cent Hypaque introduced through the ut matic injector nd n aorticopulmonary septal defect 5 cm in longitudinal diameter w demonstr ted I m bov the aortic val D) read ly entered the pulmonary artery from the scending aorta (Fig 4 A nd B).

A correcti operation utilizing cardiopulmonary bypass was carried out on April 19 1960 When exposed the right heart was found to be massively enlarged The communication bet een the ascend ing aorta nd pulmonary rtery was 5 by 3 cm in size nd wa located 1 cm. bove the normal pulmonic nd aortic lves. The pulmonary artery three times normal i size whereas the aorta beyond the communication wa smaller tha normal by one half The orta wa cross-clamped and opened proximal t the clamp. The defect was closed through the aortotomy using interrupted No. 3-0 silk sutures. Closure wa complete without compromise of the lumen of either essel After 15 minutes of anoxic rrest the cross-clamp was removed nd regula heart action promptly ensued

The postoperative course wa satisfactory ex cept for the development of transient atrial fibril



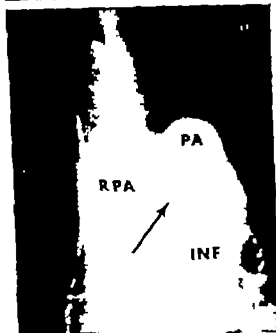


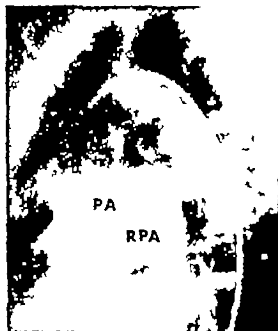
Fig. 3. A, Lateral view of right ventricular angiogram. Note the location of the dilution effect (*arrow*) just above the pulmonic valve and far anteriorly. The pulmonary artery (*PA*) is markedly dilated. The right ventricle (*RV*) and its infundibulum (*INF*) are also filled. *B*, Anteroposterior view of right ventricular angiogram. The dilution effect (*arrow*) is somewhat to the right of the usual location of a patent ductus arteriosus. *PA*, Main pulmonary artery. *RPA*, Right pulmonary artery. *INF*, Infundibulum of the right ventricle.

lation and several bouts of fever and pleuritic substernal chest pain which was relieved by sitting forward. The latter conditions were considered to be episodes of the postcardiotomy syndrome. At present, 24 months after operation, the patient has shown gradual improvement in exercise tolerance and decrease in intensity of the pulmonic second sound. Chest pain has been absent. The murmurs are unchanged, but there has been slight decrease in heart size and pulmonary vascularity on the chest film (Fig. 2,B).

Discussion

The relative infrequency of APSD is indicated by the fact that fewer than 100 cases have been reported and that the correct clinical diagnosis was not made before 1949.[9] The present case was the first recognized at Barnes Hospital. Skall Jensen found 62 cases in a review of the literature to 1956. The diagnosis was established during life in only 38 of the patients. In 28 of the 38 the presence of the APSD was not appreciated prior to the time of operation which was generally performed for a suspected patent ductus arteriosus. Thus clinical preoperative or premortem diagnosis was correct in only 10 of 62 cases.

From the foregoing it is apparent that recognition of an APSD is difficult.[11] The clinical features of the anomaly (see Table II) do not allow certain separation from (1) patent ductus arteriosus, (2) ruptured aneurysm of a sinus of Valsalva into a right heart chamber, (3) ventricular septal defect with either pulmonary hypertension or aortic insufficiency, (4) pulmonary hypertension with pulmonic insufficiency, (5) rheumatic heart disease with aortic stenosis and insufficiency, or (6) a truncus arteriosus.[4,5,11] Most of these lesions may give rise to pulmonary overcirculation and each may cause a systolic and/or diastolic murmur along the left sternal border. A late onset of the heart murmur and symptoms would point to a ruptured aneurysm of a sinus of Valsalva. A major increase in right ventricular oxygen saturation during cardiac catheterization would focus attention upon a ventricular septal defect. One should note, however, that a left-to-right shunt at the level of the pulmonary artery may cause an increase in right ventricular oxygen saturation if there is insufficiency of the pulmonic valve. To add further difficulty, the oxy-



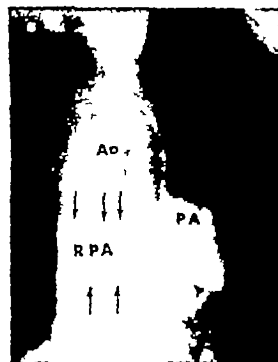


Fig 4 *A* Lateral view of the aortogram. The catheter is placed in the ascending aorta (*A*). The main pulmonary artery (*PA*) and right pulmonary artery (*RPA*) fill from the ascending aorta just above the aortic valves. *B* A teroposterior view of the aortogram. Not the marked filling of the main (PA) and right (RPA) pulmonary artery from the aorta (*Ao*) through a large defect just above the aortic valves. The arrows delineat the margins of the right pulmonary artery

gen step up due to a high ventricular septal defect may first be detected in the main pulmonary artery Passage of the catheter into the left ventricle and aorta or right ventricular angiography should afford a diagnosis in a case of ventricular septal defect with pulmonary hypertension or in a case of truncus arteriosus.

The *major diagnostic difficulty is be tween APSD and PDA*[illegible] Both lesions give rise to a left to-right shunt at the level of the pulmonary artery and may be identical in manifestations. Certain *suggestive clinical differences* have been noted however These are listed in Table III Although none of the tabulated fea tures allows a clear separation between the two lesions the presence of any atypical features *in a suspected PDA necessitates* further diagnostic evaluation

Catheterization of the right side of the heart may provide useful data of several kind [3] As previously noted location of *the increase in oxygen provides* an im portant diagnostic aid In addition the pulmonary arterial pressures and an esti mation of the magnitude of shunt flow are valuable in evaluating operability [10] Posi tive diagnostic information may be forth coming from catheterization of the right side of the heart if the catheter passes through the defect In patent ductus arteriosus the catheter enters the descend ing aorta and passes downward where as *if an APSD is present* the catheter enters the ascending aorta and moves cephalad into the aortic arch or carotid ves sels [illegible] Fluoroscopy in the lateral position will reveal the catheter to be anterior in APSD and posterior in PDA [8] Catheterization of the defect and analysis of the location of the catheter in the aorta was the method by which the correct diag nosis was reached in 8 of the 10 diagnosed cases reviewed by Skall Jensen [7]

In the case described herein the catheter did *not* enter the defect. The correct diag nosis was first suspected as a result of the unusually anterior and right sided location of the dilution *effect during angiography* of the right side of the heart This hitherto unmentioned sign is not diagnostic but was suggestive enough to warrant retro grade aortography Retrograde aortog raphy has proved to be a valuable tech

was low in 8 cases (from 8 to 24 per cent) and normal in 7 cases (from 25 to 62 per cent) A displacement curve of the Achilles reflex was recorded and the estimated muscle relaxation time was 190 to 240 milliseconds. Thus in patients with hypopituitarism the muscle relaxation time was at the upper limit of the normal values whereas this time was prolonged (250 to 620 milliseconds) in 51 of 52 patients with primary hypothyroidism It was difficult to decide whether the patients with hypopituitarism did or did not have secondary hypothyroidism On the basis of the basal metabolic rate nearly all patients were hypothyroid Contrariwise, this suggestion was contradicted by the normal muscle relaxation time and the roentgen findings which showed the normal heart size A positive response to the treatment with desiccated thyroid associated with electrocardiographic improvement as described below made possible a better evaluation of the thyroid function.

Electrocardiograms were recorded on Triplex or Sanborn apparatus with standard limb and precordial leads.

Results

A Electrocardiograms before treatment The electrocardiogram was normal in one patient in this case a hypophysial tumor was evident with signs of gonadal and adrenal cortical hypofunction whereas the thyroid function remained undisturbed In the other 19 patients, distinct electrocardiographic abnormalities which showed some common features were observed Detailed results are listed in Table I The most frequent electrocardiographic finding in 19 patients was inversion or flattening of the T waves in all limb and precordial leads. This was an early sign seen also in patients with insignificant evidence of pituitary hypofunction

The second sign frequently met with in 11 patients was a low voltage of QRS complexes in standard leads, which means that the QRS complexes were lower than 0.5 mv in each standard lead The third electrocardiographic abnormality was depression of the S-T segments, particularly in Leads V_3, V_4, and V_5 this was encountered in 13 patients. This sign was seen less frequently than were T wave changes but sometimes the depression of the S-T segments occurred at an early stage of the disease.

The prolonged Q T interval in the range of 0 40 to 0 50 second was noted in 11 patients but in 2 of them it probably resulted from previously existing acromegaly In our experience the Q T prolongation is very common in patients with acromegaly

Some flattening of the P waves was seen in 10 patients. Sinus mechanism was present in all patients, sinus bradycardia in 3 patients, and in the other patients the heart rate ranged from 60 to 90 per minute. In all patients except one with atrioventricular block the P R interval was normal

B The influence of cortisone treatment Twelve patients were available for treatment in the cortisone era. The treatment

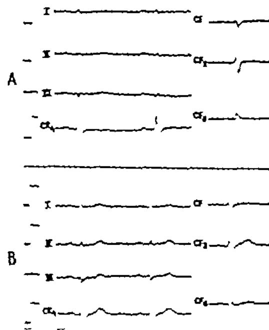


Fig 2 Case 17 C M a 48-year-old man with hypopituitarism. *A* Before treatment the following electrocardiographic abnormalities are seen low QRS voltage in standard leads, flattening of T waves in Leads I II III inversion of T waves in left precordial leads, and S-T depression in Lead CR_4. Treatment with cortisone alone did not change the electrocardiogram. (The time lines are 0 02 second.) *B* After 1 month of treatment with cortisone together with 1 grain of desiccated thyroid daily the electrocardiogram shows increase in the T waves and QRS voltage in standard leads and positive T waves in left precordial leads. The S-T segments returned to the isoelectric line

Table II Clinical features of APSD in approximate decreasing order of frequency[2,4,5,7,9,11-18]

Symptoms	*Signs*
Dyspnea on exertion	Increased pulmonic second sound
Fatigue	Wide pulse pressure
Recurrent respiratory infections	Systolic murmur along left sternal border
Physical underdevelopment	Diphasic systolic and diastolic murmur
Syncope	Continuous murmur
	Cyanosis
	Clubbing
	Diastolic murmur of pulmonic insufficiency alone
	Apical diastolic flow murmur
	Diastolic gallop rhythm
	Precordial bulge
	Right heart failure
	No murmur

nique for defining lesions of the thoracic aorta.[28] Surprisingly despite the fact that most authors agree that aortography is the method of choice in establishing the presence of an APSD there are only a few reports of the diagnosis being substantiated in this manner.[10,28-30] As demonstrated in this report (Fig. 4) this technique affords an excellent demonstration of the anatomy of the defect. Braunwald and Cornell[31] have recently described a dilution method for separating a defect of the aortic root from a patent ductus by injecting Kr[85] at several levels in the aorta and sampling in the brachial artery. This method involves catheterization of the ascending aorta. We believe that the injection of contrast into the ascending aorta provides a more certain method of establishing the diagnosis, and it certainly exhibits anatomic details not accessible to any other technique. In any instance of suspected but atypical patent ductus or suspected APSD in which catheterization of the right side of the heart fails to prove the diagnosis, retrograde aortography should be performed.[12,14,28]

The age of our patient warrants brief comment. Survival until the age of 36, as in our case is distinctly unusual. Skall Jensen found no patients over the age of 30 years. Dadds, however in surveying the earlier literature concerning this disease noted survival of 2 patients to ages 37 and 48. Neufeld and associates[4] in their review encountered 7 patients who survived beyond the age of 26. None of these patients was treated surgically and confirmation of the diagnosis was obtained at necropsy in each instance.

Most authorities now agree that APSD should be approached surgically using the cardiopulmonary bypass.[5] Early attacks without such support resulted in a high surgical mortality (about 50 per cent).[3,5,8,9,28] Unless the lesion can be demonstrated by aortography to be unusually high small and ductlike allowing ligation, an excellent approach is through the aorta or pulmonary artery with direct suture closure of the defect.

One of the presently unsolved problems in the selection of patients for cardiac surgery is the paucity of precise information in regard to the natural history and rate of progression of certain of the congenital heart lesions. In our case there was

Table III Observations suggestive of the presence of an APSD when a PDA is the presumptive diagnosis

1. A continuous, machinery like murmur heard lower and more to the midline than usual for PDA
2. A continuous or double murmur which appears to be more superficial than the murmur of a patent ductus[4,18]
3. A systolic murmur only located along the upper left sternal border associated with pulmonary overcirculation[4,18]
4. A systolic murmur along the upper or mid left sternal border followed by a separate noncontinuous early diastolic murmur[7,18]
5. Unusually severe clinical features for patent ductus[17]
   A. Dyspnea at rest or with very little effort[17]
   B. Aneurysmal dilatation of the pulmonary artery
   C. Greater cardiac enlargement than usual[9]
6. Small aortic knob[4]
7. Location of the dilution effect to the right and anterior to the usual site of emptying of a ductus, on angiocardiography performed with the tip of the catheter in the right ventricle or main pulmonary artery

no increase in the pulmonary arterial pressure nor change in the magnitude of the shunt over a period of 7 years.

The selection of patients for operation when the pulmonary arterial pressure is at systemic levels warrants brief discussion. We have adopted the view well expressed by DuShane and Kirklin that operation should be performed even in the presence of severe pulmonary hypertension if there is a continuing appreciable left to-right shunt as evidenced by an oxygen jump in the pulmonary artery by left ventricular enlargement on the electrocardiogram by overcirculation of the lung fields on the chest roentgenogram and by an overactive heart with a loud murmur. If pulmonary blood flow is reduced by closing the defect then pulmonary resistance pressure and eventually perhaps even the pulmonary vascular changes themselves may be reduced. On the other hand predominant right to-left shunting as evidenced by cyanosis at rest predominant right ventricular enlargement and absence of an oxygen increase in the pulmonary artery contraindicates operation. Closure of the defect in this situation increases pulmonary blood flow without reducing resistance and leads to greater degrees of pulmonary hypertension and right heart failure. The presence of a continuing large left to-right shunt in our patient indicated that there was a reasonable chance that an operation would be successful despite the pulmonary hypertension at systemic levels. To date (24 months after operation) the results have been gratifying.

Summary

(1) A case is reported of successful repair of an aorticopulmonary septal defect despite pressures at a systemic level in the pulmonary artery. (2) The correct diagnosis was first suggested by the location of the dilution effect in the pulmonary artery on angiography and was confirmed by retrograde aortography. (3) The clinical and catheterization features which are useful in the recognition of aorticopulmonary septal defects have been reviewed.

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Truncus insufficiency
Common truncus arteriosus with regurgitant truncus valve
Report of four cases

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Common truncus arteriosus is a congenital anomaly characterized by the presence of but a single large vessel emerging from the ventricular complex of the heart. It has been variously termed *truncus arteriosus*, *common truncus arteriosus*, and *persistent truncus arteriosus*. The true condition is rare and must be differentiated from *pseudo* truncus arteriosus, which involves pulmonic atresia, and from aortic atresia with a patent ductus arteriosus. In true persistent truncus arteriosus there must be no evidence of a remnant of a second emergent arterial trunk. From 1932 to 1961, 42 cases of true truncus arteriosus were autopsied at The New York Hospital. Of these, we are reporting 4 which have striking anatomic and clinical features associated with insufficiency of the valve of the common trunk.

Case material

Case 1. L. R., a 4-week-old girl, was admitted to the hospital with the chief complaint of a weak cry and rapid respirations. She had not gained beyond her birth weight of 3,360 grams. Cyanosis was not noted.

Physical examination revealed a thin baby in respiratory distress with a phonic cry. The pulse was 200 per minute and respirations were 60 to 80 per minute. The heart was markedly enlarged to the left with bulging of the precordium. The point of maximal impulse was diffuse and a systolic thrill was felt over the apex. The heart sounds were indistinct; however, a Grade 3 harsh, precordial, systolic murmur could be heard over the entire chest, followed by a diastolic component in the second left intercostal space. The blood pressure measurements were not recorded; *peripheral pulses* were strong. There was slight cyanosis. Scattered fine rales were heard at both lung bases; the edge of the liver was palpated 3 cm. below the right costal margin.

Laboratory tests showed a hemoglobin of 13.6 Gm. with 3.6 million red blood cells. The ECG indicated left ventricular hypertrophy and right atrial enlargement. Fluoroscopy and x-ray films showed a considerably enlarged heart with an *especial prominence of the left ventricle*, a wide basal shadow, and greatly increased pulmonary vascular markings (Fig. 1).

The child's condition did not improve after digitalization and antibiotics, and she died on Aug. 18, 1950, at the age of 5 weeks.

SUMMARY. The patient was a slightly cyanotic infant with a noiseless cry, increased pulmonary blood flow, predominant left-sided but also right-sided cardiac enlargement, and systolic and decrescendo diastolic *murmurs* at the base. She died in heart failure.

Postmortem examination revealed a truncus arteriosus with four thickened, rolled, deformed and incompetent cusps at the origin of the great artery (Fig. 2). This single great artery arose equally from both ventricles, overriding a ventricular

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Fig. 1. Case 1. Roentgenogram of chest. Note cardiac enlargement, wide base of heart, and increased pulmonary vascularity.



Fig. 2. Case 1. View of fixed specimen showing truncus and deformed valve.

septal defect that measured 4 mm. in diameter. The coronary arteries arose from the base of the single vessel. The main pulmonary artery originated as branch from the left lateral aspect of the truncus, 1.5 cm. from the base of the heart. It divided immediately into the right and left pulmonary arteries (Type 1, Edwards classification[1]). The heart weighed 80 grams (expected, 20 grams). Both ventricles were hypertrophied and dilated. In the fixed state, the right ventricle measured 7 mm., and the left, 8 mm. The ductus arteriosus was absent. Microscopically the heart was unremarkable apart from thickening of the truncus valve cusps.

The lungs together weighed 60 grams (expected 50 grams); the cut surfaces were dark red and showed indistinct alveolar architecture. Numerous small hemorrhages were scattered throughout the subpleural areas, and microscopic examination showed many areas of intra-alveolar hemorrhage and edema.

Final diagnosis. Common truncus arteriosus arising equally from both ventricles and with biventricular enlargement; quadricuspid truncus valve with insufficiency; origin of common pulmonary trunk from left side of the truncus.

Case 2. B.S., a baby boy, was admitted to the hospital on Nov. 3, 1954, at the age of 4 days, with a chief complaint of very hoarse cry and marked cyanosis. The history was significant in that the mother had been exposed to rubella during the third or fourth month of gestation. Painless, scant vaginal bleeding had occurred daily during the first trimester. The mother had a heart murmur but had been told by her physician not to worry about it; the father had been disqualified from military service because of heart disease of unknown type.

Physical examination revealed a small, diffusely cyanotic baby with a left precordial bulge. The apical impulse was between the mid-clavicular line and the anterior axillary line in the fifth intercostal space. A strong systolic thrill was palpable over the apex. A Grade 3 systolic murmur was heard over the entire precordium, loudest in the fourth intercostal space to the left of the sternum and transmitted throughout the lung fields and also into the neck. S_2 was louder over the left than over the right second intercostal space and was not split. No rales were heard. The liver was palpated 2 cm. below the costal margin. The peripheral pulses were considered to be normal. Blood pressure in the arms and legs was 80/60 mm. Hg.

Laboratory tests on admission showed a hemoglobin of 14.7 Gm., and a red blood cell count of 5.5 million. Fluoroscopy showed a uniformly enlarged heart and increased pulmonary vascular markings. The base was equally wide in the frontal and oblique projections. The right ventricle w



Fig. 3. Case 2. View of fixed specimen. Truncus and thick valve seen below; right ventricle.



Fig. 4. Case 3. Roentgenograms in the frontal (*top*) and right (*center*) and left (*bottom*) anterior oblique projections. Cardiomegaly wide basal shadow in all views, and engorged pulmonary arterial tree are seen.

larged n all ews. A S-shaped urv ture of the esophag show by bari m llow tributed t either a double aortic arch or bnormally lo ated, retroesophageal vessel. X-ray examination confirmed these findings. The ECG showed right axis deviation nd right tricular dominance both considered to be normal for newborn infa t.

Congestiv heart failure ith râles nd hepa tomegaly developed on the eighth day. The patient w d g talized over 12 hou period nd was given mercurial diuretic and ygen, but he died on the tenth day of lif

SUMMARY. The patient was a cy otic newborn inf t w th hoarse cry increased pulmonary blood flow predomina t right entricular enlargement nd ystolic thrill nd murmur. He died in heart f il re.

Postmortem examination showed the heart t be remarkably enlarged. A ommon truncus arteriosus overrode high, 5-by 9 mm. entricular septal defect ar l originated almost excl sively from the right entricle. The truncus al had three ps, ach nodular thickened and deformed (Fig. 3). T o oronary rteries, both small but patent arose from the common truncus. Both pulmonary arteries arose separately from the com mon truncus immediat ly bov the l (Type 2, Ed ard lassification). The right and left om mon carotid arteries arose separat ly the right subcla ian artery originated distal to the left sub cla ian artery nd crossed behind the esoph gus. There w patent foramen ov le that measured 7 mm. in diameter. There w slight gr lar thickening of the f ee edges of the leaflets of the tric pid nd m tral l es. The heart and lungs together eighed 124 grams (expected 75 gr ms) the heart was enlarged, primarily be se of right entricular hypertrophy nd marked dilatation. The right nd left tricles measured 5 and 4 mm. respectively.

Associated nomalies w re found in the g stro intestinal tract. The cecum was high i the right pper quadra t the small bowel, the cecum, ascending colon, nd proximal portion of the t an erse colon w re not ttached to the posterior wall but lay free i the bdominal ca ty

Microscopic examination howed moderat pat hy telectasis of both lungs, few petechiae in the epicard m nd small, pat hy hemorrhages in both kidneys.

Final diagnosis Common truncus arteriosus arising hiefly from the right entricle with marked right entricula dilatation and hypertrophy tricuspid incompetent truncus al separate origin of right nd left pulmonary arteries from base of truncus. Anomalous, retroesophageal right subcla ia artery

Case 3. S.M. 4-week-old girl was adm tted to the hospital on Feb. 4 1955, because of difficult respiration. Wheezing cough, and breathlessness, especially when she was sucking and lying flat, had been noted from 2 weeks of age. She perspired ex essively and experienced spells of ga ping respi ration. No cy nosis was noted.

Physical examination disclosed this infant in acute respiratory distress with hacking cough and with retraction of the suprasternal notch and

intercostal spaces. Slight cyanosis was evident only when she cried. A precordial bulge was noted, and the heart was enlarged to the anterior axillary line. A faint systolic thrill was felt, and a Grade 3 harsh, systolic murmur was heard over the entire precordium, best at the apex, with transmission to the axilla and posterior chest. At the right base the systolic murmur became continuous with a decrescendo diastolic murmur. S_2 was loud and pure on the left. Peripheral pulses were strong, and the pulse pressure did not seem to be abnormally wide. No rales were heard. The edge of the liver was palpated 3 cm. below the right costal margin.

Cardiac fluoroscopy and x-ray films revealed enlargement of all four chambers. The base was wide, the pulmonic segment concave, and the lung fields were hypervascular. The aorta arched to the right (Fig. 4). The ECG showed changes consistent with left ventricular hypertrophy and strain or myocardial damage.

The diagnosis of persistent common truncus arteriosus was made. Initially she responded to treatment for heart failure, but signs of increasing congestion on the left and right sides appeared, and despite 4 months of intensive therapy in the hospital she died at the age of 7 months.

SUMMARY. The patient was minimally cyanotic infant with excessive pulmonary blood flow, predominant left ventricular hypertrophy, a broad cardiac base with pulmonic concavity, and systolic and decrescendo diastolic murmurs at the base of the heart. She died in heart failure.

At postmortem examination the diagnosis of common truncus arteriosus was confirmed. A large common vessel arose primarily from the right ventricle above a ventricular septal defect that was 8 mm. in diameter. The four leaflets of the semilunar valve cusps of the truncus arteriosus valve were thickened, rolled, and irregularly nodular (Fig. 5). At a distance of 5 mm. from the base of the truncus, the pulmonary artery separated from the main vessel, which arched to the right and continued as the aorta (Type 1, Edwards classification). The coronary arteries originated from the ... posterior ...al sinuses. The heart weighed 60 grams (expected 31 grams). There was hypertrophy of the walls of both ventricles; the right measured 7 mm. and the left 11 mm. Dilatation of the left atrium and right ventricle was noteworthy.

Microscopically the cusps of the truncus valve were thickened by edematous fibrous tissue and contained several foci of dense collagen.

Together the lungs weighed 160 grams (expected, 81 grams). The left lung was compressed by the large heart; microscopic examination showed chronic passive hyperemia characterized by "heart failure cells" in both lungs.

Final diagnoses: Common truncus arteriosus arising chiefly from right ventricle, with left and right ventricular hypertrophy; quadricuspid insufficient truncus valve; origin of the pulmonary trunk from common truncus. Right aortic arch.

Case 4. L. L., a 1-day-old girl, was admitted to the hospital on Aug. 14, 1959, because of cyanosis and respiratory distress that had been present since birth.

Rapid respirations with subcostal and xiphoid retractions during inspiration were observed. Slight cyanosis, not unusual for a newborn infant, was seen in the nail beds but not in the skin. Her cry was feeble. A precordial bulge was noted to the left of the midline, and the lateral border of cardiac dullness was in the anterior axillary line. The point of maximal impulse was forceful and diffuse. A systolic thrill was felt at both the base and the apex. A single S_2 was clearly heard in the second left intercostal space, but not so well on the right. A Grade 4 harsh, systolic murmur was heard to the left and the right at the base and down the left sternal border. A Grade 2 harsh systolic murmur was heard at the apex and a Grade 2-3 blowing diastolic murmur along the left sternal border from the base to the apex. A systolic murmur could be heard over the lung fields posteriorly. The femoral pulsations were bounding; the blood pressure in the right leg was 100/40 mm. Hg; in the right arm the systolic pressure was 100 mm. Hg and no diastolic measurement could be determined. Strong aortic pulsations were palpated in the abdomen. The lungs were clear to percussion and auscultation except for a few inspiratory rales at both bases. The edge of the liver was palpated 3 to 4 cm. below the right costal margin.

The ECG was abnormal for a newborn infant; there was evidence for right atrial enlargement, marked left ventricular hypertrophy, and an incomplete right bundle branch block. Fluoroscopy and roentgenograms in the frontal and both oblique projections showed an increased cardiothoracic ratio due chiefly to left ventricular enlargement. The shadow of the base was wide, especially on the right. The main pulmonary artery could not be visualized, but the pulmonary vascularity was considered to be normal. Barium swallow outlined a right aortic arch and a retroesophageal vessel (Fig. 6). Oximetry several days after the infant was admitted to the hospital showed a capillary oxygen saturation of 80 per cent.

Diagnoses that were considered included aortic



Fig. 5. Case 3. Thickened nodular truncus valve above ventricular septal defect.



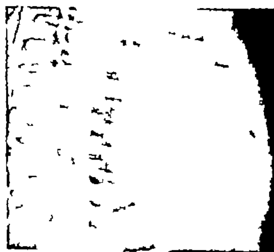




Fig. 6 Case 4 Roentgenograms in frontal (*top*) and both oblique projections show dilated basal shadow in all views with right aortic knob. Note in oblique views the anterior displacement of the esophagus by retroesophageal vessel. Enlargement of the heart and increase in lung vascular markings.

sufficiency truncus arteriosus with semilunar valve anomaly and aortic septal defect. Selective aortography was planned after intensive and rapid treatment for heart failure. However her condition deteriorated and she died on the sixth day of life.

SUMMARY The patient was a slightly cyanotic newborn infant with weak cry average pulmonary vascularity marked left ventricular hypertrophy systolic and decrescendo diastolic murmurs at the base of the heart and wide pulse pressure. She died in heart failure.

Postmortem examination revealed a persistent truncus arteriosus with an incompetent truncus valve. The large single vessel overrode both ventricles equally. It arched to the right and crossed behind the esophagus to become left descending aorta. At the base of the dorsal aspect of the truncus the orifices of the right and left pulmonary arteries were separate but close together (Type 2 Edwards classification). Four thickened, rolled semilunar cusps constituted the grossly insufficient valve (Fig. 7). The coronary arteries had a normal origin and distribution. The heart and lungs together weighed 100 grams (expected, 67.4 grams). Both ventricles were dilated, and the left one was markedly hypertrophied the walls of the left and right ventricles measured 8 and 4 mm. respectively. There was a high ventricular septal defect, 8 mm in diameter.

Other abnormalities included bilateral, bilobed lungs with four pulmonary arteries and veins. Acute patchy hyperemia and hemorrhages were present in both lungs.

Final diagnosis Common truncus arteriosus arising from both ventricles with predominant left ventricular hypertrophy quadricuspid, incompetent truncus valve; separate origin of the right and left pulmonary arteries from base of truncus. Right aortic arch. Bilobed lungs.

Discussion

The four cases presented show many findings that are characteristic of but not specific for truncus arteriosus.[1-9] The anatomic and clinical variations described are within the range of those reported in other series of such cases. The clinical features which suggested a common truncus arteriosus were minimal cyanosis in a baby with cardiac enlargement, a wide base of the heart in all views on the roentgenograms, and exaggerated pulmonary vascular markings. A concavity was noted where the main pulmonary artery would be expected. Incompetency of the truncus valve was suggested by a decrescendo diastolic murmur in the second left intercostal space and along the left sternal border. Left ventricular enlargement predominated in 2 infants with equiventricular origin of the common trunk. The truncus arose chiefly from the right ventricle

in the other 2, one of whom had predominant right ventricular hypertrophy and the other hypertrophy of both ventricles. In two of the babies there was a right aortic arch

These 4 cases show a striking similarity of the lesions involving semilunar cusps of the truncus valve In each instance, the cusps were thickened nodular deformed and insufficient grossly Lesions of the cusps per se have been described infrequently in the reports of persistent truncus arteriosus however thickened nodular" valve cusps have been noted.[6-14] Roos,[11] in particular made especial mention of the deformed cusps of the truncus valve

Motta ascribed lesions of this type involving the heart val es to what he termed chronic fetal endocarditis." Roos on the other hand believed that such alterations could be explained on the basis of an arrest in normal development comparable to that manifested in the formation and torsion of the aorticopulmonary septum He pointed out that the bulbar swellings of the embryo which are the precursors of the cusps, are composed of masses of losely packed cells. As the embryo grows, the semilunar valves become progressively less cellular until about the fifth month when their appearance closely approaches the changes he described.[11] Support for the concept of developmental arrest was provided by the



Fig 7 Case 4 View of left entricle septal defect common truncus, and abnormal al e.

case reported by Feller[1] sections through the deformed semilunar valves had a microscopic appearance similar to that of the semilunar valve of a 5-month-old embryo. Sections through the valves ex amined by Roos and Feller and in the present 4 cases, showed no evidence of an inflammatory process.

To the best of our knowledge, no clinical significance has previously been attached to these deformed cusps and no clinicopathological correlations have been made. In 3 of the 4 cases reported herein the diastolic murmur was that classically ascribed to aortic insufficiency Feller[17] mentioned a diastolic murmur in one of his cases, but did not correlate it with the valvular deformity

In this group of infants with insufficiency of the truncus valve the murmur was heard at the base and along the left sternal border to the apex and had the decrescendo quality as well as the location and transmission of the murmur associated with incompetency of the semilunar valve.

The decrescendo diastolic murmur that follows the systolic murmur is to be distinguished from the continuous murmur which Taussig[8] describes as one of the most characteristic findings in pseudo truncus arteriosus. That murmur may be present at birth and is dependent on the continuous flow of blood from the single arterial trunk through the vessels of collateral circulation to the pulmonary arterial bed Furthermore, this continuous murmur may be heard almost anywhere over the chest if especially loud it may be heard over both lungs and often is louder posteriorly than anteriorly In patients with pseudo truncus arteriosus the pulmonary vascularity may appear to be a erage or diminished but is rarely excessive in amount, as n these patients with true truncus arteriosus. If the murmur is maximal over the base of the heart to the left of the sternum differentiation from a patent ductus arteriosus or aortic septal defect would be required Since the other clinical features in these three types of aorticopulmonary shunt may also be quite simila differentiation would best be accomplished by means of selective retrograde aortography with the tip of the catheter at the base of the aorta

Summary

The clinical and pathologic findings in 4 cases of persistent truncus arteriosus associated with thick nodular incompetent semilunar valves are described. Review of the literature and theories of pathogenesis are presented.

Diagnosis during life of common truncus arteriosus with truncus insufficiency is suggested by a decrescendo diastolic murmur along the left sternal border in a minimally cyanotic infant with cardiac enlargement, increased pulmonary vascularity, and a wide heart base in frontal and oblique roentgenographic views. Selective retrograde aortography should confirm the diagnosis.

Addendum

Since this paper was submitted for publication a fifth case of truncus insufficiency was studied at our hospital. The baby was born here, went into heart failure in the first week, and came to postmortem examination at 1 month. The phonocardiogram, angiocardiogram, and selective right ventricular angiocardiogram, as well as the physical findings, x-ray examination, and electrocardiogram, were all in keeping with the features described in this report.

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Table I. Electrocardiographic findings in 20 patients with hypopituitarism

Number	Patient	QRS voltage	T waves	S-T segments	Others
1	J Z	Normal	Inverted	Depressed in V_3, V_4, and V_5	
2	G Z	Low	Inverted	Normal	Q-T 0.47 sec.
3	P W	Low	Flat	Depressed in II, III, V_3, V_4, and V_5	Q-T 0.42 sec.
4	N J	Low	Flat	Depressed in V_3, V_4, and V_5	Q-T 0.40 sec.
5	C J	Low	Flat or inverted	Depressed in CR_4	Q-T 0.44 sec.
6	C.S.	Normal	Flat	Depressed in V_3, V_4, and V_5	
7	D L.	Normal	Inverted	Depressed in V_3, V_4, V_5, and V_6	Q-T 0.44 sec.
8.	M A.	Low	Flat	Depressed in CR_4	Q-T 0.42 sec.
9	S.F	Low	Flat	Normal	
10	T K.	Low	Flat	Depressed in CR_4	A-V block, Q-T 0.50 sec.
11	A.J	Normal	Flat	Normal	Q-T 0.44 sec.
12.	T.E.	Low	Flat	Normal	Q-T 0.42 sec.
13	P Z.	Normal	Flat	Normal	Q-T 0.44 sec.
14	F Z.	Low	Flat or inverted	Normal	
15	G.M	Normal	Flat	Depressed in CR_4	
16	M T	Low	Inverted	Depressed in V_3, V_4, and V_5	
17	C.M	Low	Flat or inverted	Depressed in CR_4	Q-T 0.41 sec.
18	S.J	Normal	Inverted	Depressed in CR_4 and CF	
19	Z.A.	Normal	Flat	Depressed in V_3, V_4, V_5, and V_6	
20	K M	Normal	Normal	Normal	

was started with cortisone alone in these 12 patients but subsequently they received combined treatment with cortisone and desiccated thyroid.

In the course of cortisone treatment with a daily dosage of 50 mg. at the beginning, then 25 to 12 mg. daily, a significant clinical improvement followed in all patients. The electrocardiograms recorded within 7 to 14 days of treatment in 5 of 12 patients showed a striking improvement. Positive T waves appeared in place of the previously negative T waves, and lowered S-T segments returned to the isoelectric line. In cases with Q-T prolongation a shortening of this interval occurred. Thus, in 5 patients the abnormalities completely disappeared and the electrocardiograms became normal. An example of this is shown in Fig. 1.

Treatment was stopped after a few months in the 5 above-mentioned patients, and thereafter the above-described electrocardiographic changes gradually reappeared. When comparing, we found some correlation between hormonal data and the electrocardiograms. Improvement in the electrocardiograms during cortisone treatment occurred in patients in whom signs and symptoms of gonadal and adrenal cortical hypofunction existed, but the thyroid function remained undisturbed. In this group the I^{131} uptake was within the normal limits and ranged from 28 to 62 per cent, and the basal metabolic rate was normal in 2 patients and low in 3 others (−22, −18, and −16 per cent). Clinically, there was no further amelioration when desiccated thyroid was added to the cortisone treatment.

In the other 7 patients with anterior pituitary insufficiency, the electrocardiogram was not affected during cortisone treatment in spite of an increased cortisone dosage which reached 100 mg. daily.

C. The influence of combined cortisone and desiccated thyroid treatment. In 7 patients with hypopituitarism in whom treatment with cortisone alone had no influence on the electrocardiogram, a combined treatment with 25 mg. of cortisone daily and desiccated thyroid was started. The doses of thyroid were gradually increased under careful clinical and electrocardiographic control. Because small doses of desiccated thyroid of 1 grain daily failed to improve the electrocardiograms, the doses were increased to 2 or 3 grains daily. Using this dosage during 10 to 14 days, we found a

Arteriovenous fistula of the kidney

Case report

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Arteriovenous fistula of the kidney is a unique entity that is characterized by hypertension and cardiovascular complications in a high percentage of the cases. The diagnosis can readily be made by finding a thrill and or bruit over the afflicted kidney. Inasmuch as operation is usually curative arteriovenous fistula of the kidney should be kept in mind in ascertaining the causes of hypertension.

Intrarenal arteriovenous fistulas whether congenital or acquired are rare. We were able to find only 22 cases besides our own (Table I). Of these, only Vest's case[11] and our own resulted from renal surgery. Most of these cases were reported since 1951 which indicates a current general awareness of the diagnostic features of intrarenal arteriovenous fistula.

Case report

H F 50-year-old married woman was admitted to Hempstead General Hospital on July 5 1959 complaining of intermittent pain in the lower abdomen of 6 months duration. She stated that the present attacks were similar to those sustained 10 years ago, which culminated in the removal of part of her right kidney because of calculi. In addition to the above-mentioned symptoms, she had suffered for the past 6 months from easy fatigability, syncope and slight shortness of breath.

Personal communication with her surgeon disclosed that no thrill was present in the right kidney at the time of operation 10 years ago.

On physical examination, the patient was found to be a thin woman who appeared to be her stated age and in no acute distress. The significant findings were as follows. The blood pressure in each arm was 140/70 mm. Hg. The pulse rate was 84. There was Grade 2 precordial systolic murmur to the left of the sternum which increased in intensity after exercise. The only other positive finding was a continuous thrill over the right upper abdomen and back. The latter was discovered on routine physical examination by one of us (E.E.S.). The thrill changed in intensity when the patient was placed in different positions, and it did not seem to be associated with the operative scar. Heard over the same area was a continuous murmur which seemed to be classic for systemic arteriovenous shunt.

Laboratory data. The hemoglobin was 12.6 Gm. The red blood cell count was 4 1 million the white blood cell count was 5,800 and the differential was normal. The determinations of acid and alkaline phosphatase nonprotein nitrogen and serum uric acid were normal.

A chest x-ray film disclosed the heart to be appreciably larger than was noted on the postoperative film taken 3 months later (Fig 1). The electrocardiogram, both preoperatively and postoperatively was read as showing normal axis with vertical heart position.

Intravenous and retrograde pyelograph revealed bilaterally functioning kidneys with an irregularity of the lower right renal pelvis. Two renal calculi were present in this region one the size of a pea at the level of the transverse process of the

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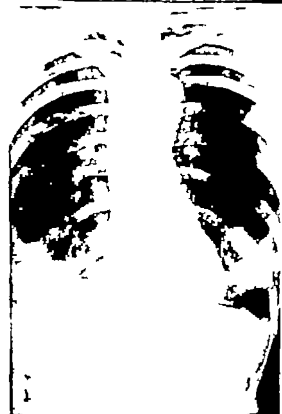


Fig 1 Preoperativ (*top*) and postoperati (*bottom*) x-ray films, showing diminution in heart size 3 months after operation

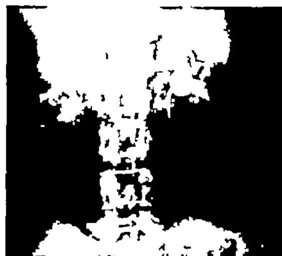


Fig 2. I tra enou pyelography howing irregularity the right lower renal pelvis and two calculi.



Fig 3 I travenous angiogram. Marked dilatation and tortuosity of the right renal artery Large sac cular collections of contrast media withi kidney

second lumbar ertebra, nd smaller one just below it (Fig 2). Radiographic exposure of the kidneys during angiography revealed markedly dilated, tortuous right renal artery with large sa cular collections of contrast material withi the kidney (Fig 3). Further confirmation by direct aortography or catheterization of renal vein was thought not to be necessary

By means of an incision in the right flank the kidney was exposed It appeared to be normal i size position, and mobility The renal artery was soft and markedly dilated. A pronounced intra-renal thrill was felt t the lower pole of the kidney this thrill could be obliterated by occluding the renal artery Nephrectomy was performed and the patient postoperati e course was uneventful.

Re-evaluation 3 months fter operation revealed the following significant findings (1) bsence of thrill in the right flank (2) absence of former pain in lower abdomen and easy fatigability (3) blood pressure of 112/75 mm Hg in each arm in contrast to the preoperative reading of 140/70 mm. Hg (4) resting pulse rate of 68 instead of 84 before nephrectomy and (5) dimin tion i heart size on the x-ray film (Fig 1).

The electrocardiogram was unchanged

The systolic murmur t the left sternal border was also unchanged The significance of this is unknow t the present time but cardiac catheterization has been advised

Pathology report. "The specimen consists of totally removed kidney measuring 11×7×4 cm



Fig 4 Demonstra ion of fistula. Contrast medium ha been injected int the renal vein and ha immediately entered the renal artery through the fistula.



Fig 5 Both renal essels ha been i jected nder pressure. The contrast material fills the large saccular sinuses throughout most of the renal parenchyma.

The pelvis is distorted and the major vessels are altered in position entering the kidney near its lower pole. The capsule strips ith difficulty The are over the lower pole is firmly adheren and has calcific consistency Dissection reveals saccular dilated artery communicating w th dilated ei via short 3 mm fist la Fluid injected int either vessel passes freely t the other Demonstration of this phenomenon was obtained radiographically by injecting radio-opaque medium int the vein. (See Fig 4) "The remaining kidney parenchyma displays the usual architecture. The cortico-medullary ratio is well maintained. The renal calyces pelvi and portion of the ureter are not remarkable

Pathophysiology of renal fistula

Like any systemic arteriovenous fistula a renal arteriovenous fistula shunts blood from the systemic arterial circu t to the enous system and the general effects of ncreased blood volume left ventricular hypertrophy and eventual cardiac em barrassment are common to both The renal arteriovenous fistula is characterized further by its physiologic effect upon the

Table I. Summation of cases of intrarenal arteriovenous fistulas

Age (yr.)	Sex	Symptom	B.P. on admission (mm. Hg)	Cardiac failure	Cardiac enlargement	Thrill in flank
28	M	Dyspnea	160/80	Yes	Yes	Yes
29	M	Dyspnea	220/120	Yes	Yes	Yes
60	M	Hematuria	160/60	No	No	No
47	M	Hypertension	200/100	Yes	Yes	Yes
29	M	Dyspnea and fatigue	180/110	Yes	Yes	Yes
26	M	Dyspnea	210/130	Yes	Yes	Yes
3	F	Hematuria				
7	F	Headache	146/110	No	No	Yes
22	M	Dyspnea	160/70	Yes	Yes	Yes
19	F	Dyspnea	170/80	Yes	Yes	Yes
66	F	Hematuria and pain in flank	140/70	No	No	Yes
63	M	Dyspnea	140/60	Yes	Yes	Yes
18	M	High blood pressure	200/?			
35	M	Edema and fever	140/90	Yes	Yes	Yes
32	F	Vertigo and headache	180/100	Yes	Yes	Yes
68	M	Hemoptysis	130/80	No	No	No
42	M	Palpitation and fatigue	174/84	No	Yes	Yes
30	F	Abdominal pain and dyspnea	180/80	Yes	Yes	Yes
39	F	Headache and fatigue	206/110	Yes	Yes	Yes
53	M	Hematuria	230/120	Yes	Yes	Yes
62	M	Palpable mass	206/110	Yes	Yes	Yes
29*	M	Hematuria and blurred vision	210/145	No	No	Yes
50	F	Fatigue and abdominal pain	140/70	No	Yes	Yes

*Diagnosis not confirmed by examination of tissue.

involved kidney, specifically the production of a Goldblatt kidney. Holman and Taylor have shown that the flow of blood distal to a fistula is decreased and may even be reversed, depending upon the size of the shunt. The pulse pressure is also decreased. These findings have been confirmed by Robertson, Dennis, and Elkin and also by Lasher and Glenn. Both decreased renal blood flow and decreased pulse pressure per se have been listed as causative factors in the production of the Goldblatt kidney. Certainly, the frequency of hypertension in the cases summarized in Table I suggests that such a mechanism in fact does prevail. Consequently, the patient who has an arteriovenous fistula of the kidney has two components operative in his disease, namely, cardiac embarrassment from the systemic effect of his fistula, and a compounding of this embarrassment by the hypertension associated with a Goldblatt kidney. Milloy and associates[4] wrote an excellent review of the physiology of the condition, and Scheifley[23] has also written one more recently.

Comment

Since renal arteriovenous fistulas are characterized by their own pathophysiologic sequelae, we believe that they should be in a class by themselves. They may be conveniently subdivided into congenital or acquired. The latter may be further classified as traumatic, postoperative, infectious, or neoplastic.

It should be emphasized that a renal arteriovenous fistula should not be confused with either a stump fistula (after nephrectomy) or a simple renal artery aneurysm. These are not productive of hypertension.

Conclusion

1. A rare case of arteriovenous fistula of the kidney which resulted from renal surgery is presented.

2. The physiologic effects (largely circulatory) are twofold: (a) those which result

Type	Nephrectomy	Outcome (cardiovascular)	Author	Date reported
Congenital	No	Died	Varela	1928
Congenital	Yes	Cured	Rieder[7]	1942
Congenital	Yes	Cured	Pearse and MacMillan	1947
Congenital	Yes	Cured	Adams[9]	1951
Acquired-cancer	Yes	Cured	Hamilton, et al[10]	1953
Acquired-bullet wound	Yes	Cured	Pelot, et al[11]	1954
Acquired-postoperative	Yes		Vest[12]	1954
Acquired-stab wound	Yes	Cured	Baron and Koenemann[13]	1955
Acquired-bullet wound	Yes	Cured	Kirby et al[14]	1955
Congenital	Yes	Cured	Slominski-Lawa, et al[15]	1956
Acquired-cancer	Yes	Cured	Myhre[16]	1056
Congenital	Yes	Cured	Bohne and Henderson[17]	1957
Congenital	Yes	Cured	Gollmann[18]	1958
Acquired-infection (bacterial endocarditis)	Yes	Cured	De Vernejoul, et al[19]	1958
Acquired-stab wound	Yes	Good, but B.P slightly elevated	Milloy et al	1958
Congenital	Yes	Cured	Hoffman and Fontoura[20]	1958
Acquired-bullet wound	Yes	Cured	Scheifley et al[21]	1959
Acquired-injury ?	Yes	Cured	Scheifley et al[21]	1959
Acquired-cancer	Yes	Good but B.P slightly elevated	Scheifley et al[21]	1959
Congenital	Yes	Cured	Grace, et al[22]	1960
Acquired-cancer	Yes	Cured	Abbott, et al[23]	1961
Congenital	N	Unchanged	Brink[24]	1960
Acquired-postoperative	Yes	Cured	Mangiardi, et al	1962

from systemic arteriovenous fistula per se, and (b) those which are produced by the Goldblatt phenomenon

3 Routine palpation and auscultation of the renal areas should facilitate the finding of such fistulas. Confirmation of the diagnosis can be obtained by angiocardiography (as in our case) and if necessary b direct aortography and or catheterization of a renal vein Since operation is curative early diagnosis before irreversible hanges take place is mandatory

To the usual correctable causes of hypertension we wish to suggest the add tion of arteriovenous fistula of the kidney

W wish gi credit for valuable assistance in be preparation of this paper to Dr Ephraim J Felderman, Pathologist nd Dr Arnold Freed, Roentgenologist Hempstead General Hospital, Hempstead N Y

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Clinical pathologic conference

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Clinical abstract

History. This 56-year-old white man, a production control manager, was essentially in good health until June 1959 when on routine employment physical examination he was told that he had high blood pressure. Apparently no treatment was instituted at that time. The patient was asymptomatic except for occasional numbness of the ulnar aspect of the left hand and arm. In November 1959 he was hospitalized elsewhere because of pain in the chest. A diagnosis of hypertensive heart disease, coronary thrombosis and pulmonary edema was made. The patient was rehospitalized there for 2 weeks in December 1959 because of fatigue, malaise, generalized weakness, and loss of weight. He was treated for pulmonary edema and cor pulmonale. Past history included an operation on the left knee after trauma when he was 16 years old and known allergy to sulfa drugs and penicillin. The patient's mother died of cancer of the lung at the age of 72, and his father died of heart disease (etiology unknown).

In February 1960 he was first admitted to the Surgical Service of the Research and Educational Hospitals of the University of Illinois. Positive physical findings were: blood pressure of 210/120 mm. Hg in the right arm, and 146/104 in the left; moderate cardiomegaly to the left with a Grade 1-2 aortic systolic murmur; a bruit at the bifurcation of the left carotid artery and a faint bruit over the right carotid artery; diminished but palpable pulses in the neck and upper and lower extremities; edge of the liver 1 fingerbreadth below the right costal margin; and mild residual weakness of the right facial nerve since an episode of Bell's palsy in 1958. An electrocardiogram showed evidence of left ventricular hypertrophy and digitalis effect. Urinalysis was normal, specific gravity 1.015; hematocrit 44 per cent; white blood cell count 11,200; blood urea nitrogen 22 mg. per cent; A/G 5.1/2.2 Gm. per cent; cholesterol 425 mg. per cent; and electrolytes normal. He was given low-salt diet, chlorothiazide 500 mg. a day, digitoxin, 0.1 mg., and rauwolfia (Raudixin), 50 mg. daily. A left carotid arteriogram was obtained during an attempt at retrograde aortography but because the patient developed a sudden hemiparesis of the right side, the procedure could not be completed. The left carotid artery appeared to be normal to the bifurcation. The patient was given heparin, and later Dicumarol, to maintain a prothrombin time of about 20 per cent. There was gradual improvement of the hemiparesis. Electroretinography was compatible with decreased blood flow to the left eye and ophthalmodynamometry was inconclusive.

Between August and November 1960 the patient was admitted three times to a hospital elsewhere with dyspnea and cyanosis. He had noted persistent ankle edema since September 1960. Digitoxin was increased to 0.2 mg. per day. In spite of diuretics and antihypertensive drugs his response was unsatisfactory and he was admitted to the Research and Educational Hospitals for the second time in December 1960. During the preceding week he complained of tinnitus and shortly before admission he developed nausea and vomiting.

Physical examination. Physical examination revealed a well-developed, poorly nourished white man who appeared to be chronically ill. The blood pressure was 180/100 mm. Hg in the right arm, and 145/90 in the left. The pulse rate was 70, with occasional premature ventricular contractions; the respirations were 20 and the temperature was normal. Examination of the head and neck revealed slight ptosis of the left eyelid, narrowing of arterioles with A-V nicking on funduscopy, a lesion of the right paranasal skin suggestive of a basal cell carcinoma, and bilateral carotid bruits. The chest was clear. The heart was enlarged to the left, with a diffuse point of maximal impulse 3 cm. outside the mid-clavicular line in the sixth intercostal space. There was some left parasternal systolic lift. There was a Grade 2-3 systolic murmur at the apex and left sternal border and a Grade 3 systolic ejection murmur loudest at the second right interspace radiating to the neck. The abdomen was soft. The edge of the liver was palpable 3 fingerbreadths below the costal margin, smooth, and nontender. The right radial pulse was stronger than the left, both femoral pulses were weak, and pedal

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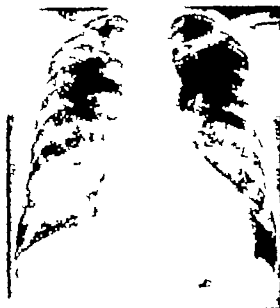


Fig. 1. X-ray photograph of chest showing the enlarged heart.

pulses were unobtainable. Deep tendon reflexes were hypoactive bilaterally, but the Babinski reflex was absent. There was 2 plus pitting edema of the feet and ankles.

Laboratory data. Admission urinalysis was normal, specific gravity 1.015; hematocrit 39 per cent; white blood cell count 8,300 with a normal differential count. Blood chemistries: Na 139, K 6.6, Cl 99, CO_2 20 (mEq./L.); blood urea nitrogen 31 mg. per cent; serum glutamic oxaloacetic transaminase 78; bilirubin 2.16 mg. per cent (direct 0.52); alkaline phosphatase 4.6 units; cephalin flocculation 1 plus; thymol turbidity 4.5 units. Serology was negative. Sputum culture grew out a moderate number of *Candida albicans*, Neisseria, and alpha streptococci. An electrocardiogram showed sinus arrhythmia with frequent premature ventricular contractions, left ventricular enlargement, and evidence of left atrial enlargement. A chest x-ray film with barium swallow showed marked increase in the cardiac size as compared to the film of February, 1960. Other findings included left ventricular predominance with pulmonary congestion and increased prominence and elongation of the aorta.

Hospital course. Digitalis was stopped and the patient was put on a low-salt diet, KCl, quinidine, ammonium chloride, meralluride (Mercuhydrin), and later chlorothiazide. His nausea, vomiting, and diarrhea subsided, and his weight decreased from 145 to 119 pounds over a 3-week period. Digitoxin was reinstituted at 0.1 mg. a day on the eleventh hospital day. Chlordiazepoxide (Librium) was later added for anxiety and depression as recommended by a psychiatric consultant. On the fourteenth hospital day the patient underwent excision of the histologically verified cancer of the paranasal region under local anesthesia. Repeat blood chemistries revealed Na 132, K 3.0, Cl 85, CO_2 34 (mEq./L.)

and blood urea nitrogen of 17 mg. per cent. Serum K rose to 4.5 with increase in supplementary KCl orally. The patient had another episode of agitated depression and was again seen by the psychiatrist. On the twenty-seventh hospital day the patient developed dyspnea and râles throughout the chest. An x-ray film showed no evidence of infiltration in the lungs. The electrocardiogram showed sinus arrhythmia with digitalis effect and left ventricular hypertrophy (Fig. 2). Within several hours the patient became unresponsive, went into shock, and died.

Discussion

DR. CALENOFF: *X-ray findings.* The chest films taken in February, 1960, showed that the heart was at the upper limit of normal. The aorta appeared to be slightly elongated. The lung fields were essentially clear. There was no calcification of the coronary vessels nor of the valves.

Ten months later, in December, 1960, the heart was significantly enlarged. The left ventricle seemed to account for this enlargement, whereas a double density that projected over the mid heart probably represented an enlarged left atrium. The aorta appeared to be more elongated than on the previous films. The pulmonary markings were somewhat accentuated and this finding would favor early congestive changes. There was no pleural effusion nor was there any definite evidence of pericardial effusion, although this could not be completely excluded. Nevertheless, in the lateral view there was an unusual density below the heart, actually between the heart and the diaphragm, strongly suggestive of a pleuropericardial effusion in this area.

With a barium swallow an enlarged and probably hypertrophied left ventricle could be made out in lateral and left anterior oblique views. There was little right ventricular enlargement since the space between the heart and the sternum was still clear. In the right oblique view the column of barium was displaced posteriorly by a tremendously enlarged left atrium. There was no enlargement of the right atrium, however.

A chest x-ray film taken shortly before the patient died showed further enlargement of the left ventricle, but the lung fields were essentially clear.

With respect to the attempted aortography, the contrast material filled the left

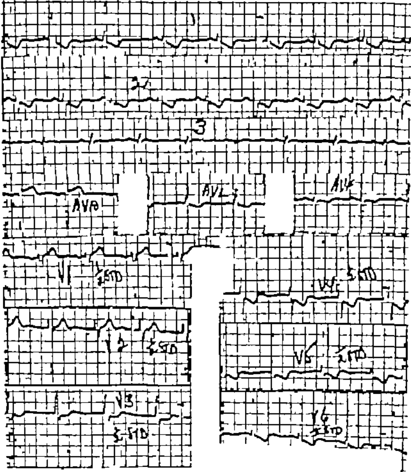


Fig 2. Normal sinus rhythm The QRS axis = 0 degrees. The T axis = 150 degrees. Rate 68 P R 0 19 QRS 0.08, Q-T 0.36 sec S-T segment is depressed and T inverted. There is evidence of lef entricular hypertrophy and digitalis effect.

carotid artery and del neated t learly up to its bifurcation However there was no dye in the aorta and none could be seen in the left vertebral artery

The onset of hemiparesis during aortog raphy points up th risk associated with the performance of angiography The introduction of catheters i to arteriosclerotic arteries carries with t the probabil ty that a small plaque ma be detached

The fact that no d e penetrated into the aorta could be explained by th possibil ty that the ort was thrombosed or that there was not enough dye to fill the vessel.

DR. FELDMAN It is rather l kel that this man uffered from hypertension, hyper tensi e heart disease probable coronary disease with or without myocardial infarc tion and finally myocardial failure. It is not likely that calcific aortic stenosis is responsible for the entire clinical picture. The absence of a characteristic loud aortic systolic murmur and the presence of di minished arterial pulsation in the neck and upper and lower extremities are factors against such a diagnosis.

The apical systolic murmur and the large left atrium shown by x-ray examination denote regurgitation of blood through the mitral orifice However it is known that such murmurs can exist in such large left hearts without organic mitral disease.

The diagnosis of cor pulmonale is not tenable because of the history of pain in the chest, hypertension and evidence of

left ventricular involvement and the absence of objective or subjective findings of chronic pulmonary disease unless it was an acute cor pulmonale resulting from pulmonary infarction However the complaints at the time of that hospitalization do not suggest such a complication

The interesting and puzzling feature of this case is the progressive impairment and inequality of his peripheral pulses, with final disappearance of some Therefore in addition to his congestive heart failure certain etiological or complicating disease entities must be considered

Coarctation of the aorta should come first for consideration Although the diminished femoral pulses fit in well the weaker left radial pulse and the lower blood pressure in the left arm are unusual features in the typical case of coarctation The same holds true for the absence of notching of the ribs, and the presence of a normal aortic knob as seen on the x-ray film To circumvent these atypical points, one could postulate that the coarctation was pre-subclavian thus compromising this vessel Under such circumstances one would expect underdevelopment of the left arm Notching of the ribs if present would occur only on the right side when the subclavian artery is not compromised and acts like a fountainhead for the collateral circulation The bruit transmitted along the carotid vessels might have originated from such a pre-subclavian narrowing and aortography could have cleared up this point, had not the attempt failed

Another feature against coarctation of the aorta is the progressive diminution of the peripheral pulses with final disappearance of some. This may occur when an infection is superimposed upon the site of the coarctation giving rise to an aortitis with final obstruction. There was no clinical evidence for such a complication in this case. Hence the evidence is against coarctation of the aorta Congenital coarctation of the abdominal aorta was thought of but not seriously so, for the same reasons.

Dissecting aneurysm of the aorta is considered next. It is possible that the episode of chest pain in November 1959 was aortic in origin This catastrophe could easily account for the difference in the peripheral pulses, and for the bruit in the vessels of the neck. If this were the case one would have difficulty in accounting for the heart failure that ensued unless the dissection produced an aortic insufficiency as a result of sagging of the aortic commissures. The protocol fails to mention the existence of a diastolic aortic murmur If it was missed at the time of his first hospital admission it probably would have been observed by someone during the final stay in this hospital considering the number of observers in a teaching medical ward The duration itself a year in this case does not oppose such a diagnosis Patients with dissection of the aorta are known to have lived longer however in such cases either a double-barrelled aorta with rupture back into the aortic lumen takes place or the dissection does not progress but heals as it were In this case, if one judges by the progressive diminution of the peripheral pulses, the processes that caused it were progressive. Hence one can hardly imagine the dissection being so active and progressive and yet lasting for 13 months. Therefore this diagnosis is not favored

Lastly thrombosis of the aorta with involvement of some of its branches, comes up for consideration and could easily account for the progressive occlusive phenomena that took place. Thrombosis of the aorta may be secondary to trauma or periaortic inflammation or it may have no apparent cause It may occur at the site of an ulcerated plaque or as a result of retrograde propagation from an embolus which has lodged at the bifurcation The latter situation is possible in this case since the patient was supposed to have had a myocardial infarct a few months before Although some of the brachiocephalic branches seem to have been involved I doubt that the symptoms and clinical course warrant the designation of Takayasu pulseless or brachiocephalic disease as described in the literature. The absence of headache vertigo ocular manifestations cramps in the upper extremities, and numbness which are symptoms usually experienced by the young female with so-called pulseless disease makes this diagnosis rather unlikely in this elderly male patient with

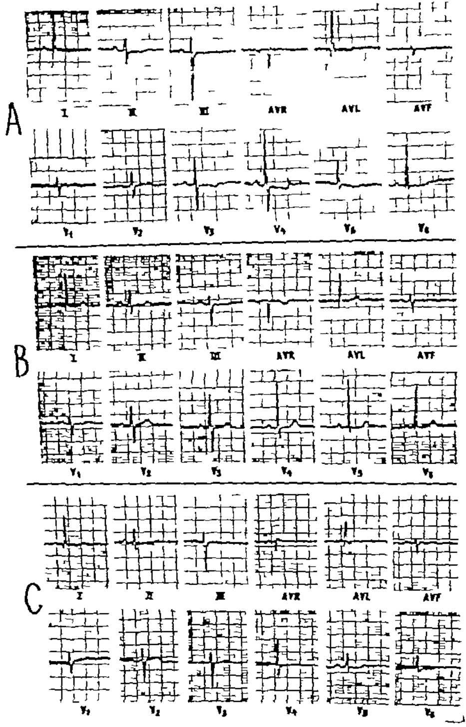


Fig. 3. Case 7. D.L., 30-year-old woman with hypopituitarism. *A*, Before treatment the electrocardiogram shows low or inverted T waves in Leads I, II, V_4, V, V, V, and depressed S-T segments in Leads V and V. Cortisone treatment alone did not improve the electrocardiogram. *B*, After combined treatment of cortisone and 2 grains of thyroid daily all abnormalities completely disappeared. *C*, After diminution of thyroid to 1 grain daily the electrocardiographic abnormalities appeared again: the T wave became low in standard and left precordial leads and the S-T segment were lower in Leads V and V.

marked involvement of the abdominal aorta and associated heart muscle failure, from which he died

That "pulseless" or Takayasu disease has been reported also in some elderly males is known. Whether we call this man's aortic disease by one name or another is just a matter of semantics. Whatever designation we employ, the etiology remains just as obscure, in spite of the increased frequency of thrombosis of the abdominal aorta and its branches in recent years. Neither can we always associate this disease with a high blood cholesterol which this man had, for low or normal cholesterol is not infrequently seen in patients with thrombosis of the aorta.

Although it is possible that the thrombosis of the abdominal aorta aggravated his hypertension by acting in the manner of a coarctation, there was little chance for this to be relieved operatively since the patient was at all times a very poor surgical risk. Besides, the process was too diffuse.

Finally, it is possible that the lower blood pressure in the left arm was not due to thrombosis of the subclavian artery but to a natural narrowing, since the blood pressure in this arm remained the same throughout the year of his illness.

DR. KRAKOWER: At the time of autopsy there was minimal edema over the sacrum and ankles. There was no excessive accumulation of fluid in any of the serous cavities, however. The heart weighed 650 grams and was clearly enlarged. The left ventricle was dilated and hypertrophied with a thickened gray white endocardium that was most marked in the septal region. There was enlargement of the left atrium. The mitral ring was widened, measuring 11.1 cm. (normal 10 cm.). Despite the dilatation of the left ventricle its myocardium measured 1.3 cm. near the apex and 2.0 cm. near the base (normal 0.8 to 1.0 cm.). However, it was the seat of extensive fibrosis which was most apparent in the anterior portion of the septum and included the atrophic appearing anterior and posterior papillary muscles as well as the trabeculae carneae of the juxta-apical portion of the ventricle. There were no mural thrombi. The aortic valve was not remarkable. The right atrium and ventricle were not very remarkable, except for some mild hypertrophy of the right ventricular myocardium, which measured maximally 0.4 cm. (normal 0.1 to 0.2 cm.). There was considerable atherosclerosis of the coronary arteries with marked narrowing and with obliteration of an area of the right circumflex.

The aorta was of interest. There was marked atherosclerosis of the sinuses of Valsalva and the widened ascending portion of the arch. Close to the transverse arch there were ulcerated atheromata with adherent thrombi. The transverse arch was likewise markedly atherosclerotic. The orifice and the immediate distal sector of the right innominate artery were wide. The orifice of the left carotid artery was somewhat narrowed by the atherosclerotic process. The left subclavian artery was profoundly narrowed at and above its point of origin for 1 cm. of the length of the vessel. There was no evident coarctation of the arch (Fig. 3). The descending arch and the whole length of the thoracic and upper abdominal portions of the aorta revealed marked ulcerative atherosclerotic changes (Fig. 4). The left renal artery was patent, but the right one was greatly narrowed by what appeared to be an old organizing thrombus for its whole length, in fact as far as its point of division into calyceal or lobar branches. The orifice of the celiac axis was narrowed by the surrounding atheromatous changes, but that of the superior mesenteric artery was wide. Starting at a level slightly below the latter artery, the remainder of the abdominal aorta and both common iliac arteries were occluded by a thrombus. The latter was recent, unattached, and bright reddish brown in color proximally, with a smooth rounded apex (Fig. 4). More distally it appeared to be progressively older, now adherent, grayish yellow in color with areas of liquefaction (Fig. 5). However, in the iliac arteries the central portion of the thrombus appeared to be recent.

Although the carotid arteries could not be dissected, their patency was tested for by injecting a saline solution after the brain had been removed. By this means there was no evidence of any gross obstruction of the common and internal carotid



Fig. 3. Transverse arch of the aorta showing wide opening of right innominate artery, narrowed orifice of the left carotid artery, and profoundly narrowed left subclavian artery (L.S.).

arteries. There were atheromatous plaques in the vertebral, basilar, and mid-cerebral arteries of the brain, but none of these vessels was occluded. The distal portions of the celiac axis and mesenteric arteries were not remarkable. The arteries beyond the obstructed iliacs were not dissected. There were no venous thromboses.

Microscopically, there was diffuse interstitial fibrosis of the left ventricular myocardium, more marked in the areas described under the gross appearances of the heart. There was considerable hypertrophy of the muscle fibers. In fact, there appeared to be an unusual degree of splitting of these fibers as may be seen in excessively hypertrophied hearts. Careful examination of sections of the aorta and its branches failed to reveal any evidence of underlying syphilitic process or of any other infectious or allergic vascular disease. The lesions were essentially those of arteriosclerosis and atherosclerosis complicated in instances by thromboses (see photomicrographs in Fig. 6).

Only those arteries with occlusions will be dealt with. The occluded circumflex branch of the right coronary artery presented an obliterated lumen occupied by vascularized connective tissue with heavy deposits of hemosiderin, clearly an index of an old organized and canalized thrombus. The left subclavian artery presented a thick, well-preserved media, permeated by prominent vessels sheathed in connective tissue which extended to the involved intima. The latter was thick, made up of hyalinized and, in places, vascularized connective tissue and associated with fresh red blood cell extravasates. Over this thick intima were the remnants of an extensive ruptured and ulcerated atheroma with retained calcific plaques. An old hyalinized thrombus with minimal organization filled much of the narrowed eccentric lumen. There was apparently a more recent accretion of thrombotic material arranged in lamellar fashion which further narrowed the lumen. Likewise in the common iliac arteries in conjunction with a thinned media and irregular loss of the elastica interna there was intimal vascularized tissue. The latter underlay a fibromuscular or more fibrous, thick intima with irregular atheromata and calcific deposits. A hyalinized thrombus was applied to the thick intima, and a freshly laminated thrombus occluded the central portion of the lumen. Near the aortic bifurcation the old thrombus in the aorta was of hyaline character showing limited organization from a thick fibrosed and atheromatous, irregularly vascularized intima. In this portion of the aorta the media in areas was totally atrophic and lost, and the adventitia was thick and fibrous. It may be added that the right renal artery, at least in the sections studied, showed marked luminal narrowing as a result of atherosclerosis, with no evidence of recent or old thrombosis.

In regard to the other organs, the lungs were rather heavy; the right weighed 730 grams and the left weighed 580 grams. They were congested, not very edematous, but there was a thin frothy fluid in the bronchi. The pulmonary arteries and their branches were clear. Microscopically there was evidence of chronic passive congestion with little edema but with considerable emphysema and interstitial fibrosis. In some instances the larger bronchi contained mucus, and their hyperemic walls were infiltrated with cells of chronic inflammatory character. The bronchioles were stuffed with purulent and mucopurulent exudate which extended into some of the alveolar ducts. There was an organizing and obliterative bronchiolitis as well and about these and extending into the interstitial fibrosed areas of the lung there



Fig. 4. Lower thoracic and upper abdominal aorta with extensive ulcerated atherosclerosis. Fresh thrombus with rounded apex protrudes from the lower unopened end of the aorta.

were in instances, appreciable mononuclear cellular infiltrates. There was chronic passive congestion of the abdominal viscera. The liver showed centrolobular atrophy with some central fibrosis. There was more fibrosis of the portal areas, associated with some tendency toward rounding and scalloping of the periphery of the lobules, with extension of the fibrous tracts irregularly into the lobules. The right kidney with the narrowed renal artery weighed 140 grams, and the left one weighed 165 grams. Its cortex was reduced in thickness to 0.4 cm., as compared with 0.6 cm. for the left. Beyond that grossly and microscopically there were no differences in the kidneys. Both showed subcapsular atrophy with heavy lymphoid infiltration. The glomeruli were large and congested. Throughout the cortices there were some streaks with a chronic inflammatory cellular infiltrate. There were no gross lesions in the brain except for some enlargement of the lateral ventricles. Microscopically, except for calcification of small vessels in the globus pallidus, there were no significant changes. In general, the arterioles showed some hypertrophy with hyalinization of some in the adrenal capsule, hepatic portal spaces and rarely the renal cortex.

This case exemplifies the diagnostic problems and complications arising as a result of diffuse and marked arteriosclerotic and atherosclerotic involvement of the whole length of the aorta and its immediate branches. Unfortunately there is no record of any physical examination prior to June, 1959, so that we cannot determine when this man's hypertension actually appeared. However, in the light of recent findings that an appreciable number of patients with so-called essential hypertension present abnormalities of one or both renal arteries, it is not too remote to believe that the basis of this man's hypertension may have been the marked arteriosclerotic narrowing of the right renal artery. If the state of the arterioles can be used as a guide, it may be that the onset of hypertension was relatively recent or in all had been relatively mild. With that as a base, the other atherosclerotic and arteriosclerotic processes may actually have been hastened and intensified. Five months after recognition that he was hypertensive



Fig. 5. The remainder of the abdominal aorta is exposed, showing the fresh thrombus superiorly and the older thrombus adherent with the cystic spaces inferiorly.



Fig. 6. All sections were stained with Weigert Van Gieson stain. *A*, Right coronary artery. Old thrombosed artery with organization and obliteration of lumen. ×20. *B*, Left circumflex coronary artery. Tangential cut shows portions of lumen to right and left and large atheromatous lesion narrowing lumen to the left. ×11. *C*, Left subclavian artery. Thick atheromatous intima appears in large part clear in photograph, with hyalinized thrombus surrounding narrow remains of lumen in the lower photograph. The darker area within the hyalinized circumferential band represents a recent accretion of thrombotic material. There is virtually no lumen in upper section of the vessel, which has been cut slightly tangentially. ×13. *D*, Right renal artery. Marked intimal fibrous thickening with atheromatous "spaces" and slit-like narrowing of the lumen; ×11. *E*, Abdominal aorta with protruding fresh thrombus. Note laminated character of the thrombus; ×13. *F*, Abdominal aorta with old thrombus. Hyalinized portion of thrombus has shrunken away from the thick fibrosed intima except to the right, where it is bound to the intima. ×13. *G*, Iliac artery. Fresh laminated thrombus fills the lumen; ×10.

he had symptoms of coronary thrombosis for which he was hospitalized. The old organized occlusion of the right coronary artery in conjunction with the marked sclerotic narrowing of the left descending and circumflex branches and the extensive myocardial fibrosis, particularly anteroseptally would be in keeping with coronary thrombosis and irregular myocardial necrosis a year or so prior to his death. However soon after that episode disquieting complications arose. One was myocardial failure. The other was an aortic arch syndrome with clinical manifestations that closely simulated those of coarctation of the aortic arch. For that reason the patient was referred to the Surgical Service of this hospital. This diagnosis was seriously enough considered that aortography via the left carotid artery was attempted. Had the patient been in better physical shape he might very well have been subjected to exploration for a coarctation although in retrospect and in the light of the ensuing events in the terminal 10 months of his life there was less certainty about this diagnosis. Nevertheless it was never excluded right up to the time of his death. In effect as it turned out there was arteriosclerotic narrowing and thrombosis without occlusion at first of the left subclavian artery which accounted for the diminished radial pulse the lower levels of systolic and diastolic pressure on the left side, and presumably in large part, the bruit heard over the area of the left carotid artery At the same time and assumedly on the basis of thrombosis rather than embolism occlusion of the distal abdominal aorta at and near the bifurcation occurred. This accounted for the reduced pulses in the lower extremities. This is an unusual set of circumstances, in that thrombosis of these two distal structures occurred almost simultaneously leading to a clinical picture not unlike that of aortic coarctation

Subsequently despite digitalis therapy cardiac insufficiency became more marked The left atrium and left ventricle enlarged. In keeping with this were the findings not only of extensive interstitial fibrosis of the left myocardium but fibrosis and atrophy of both anterior and posterior papillary muscles, an index over-all of decreasing coronary blood flow Most likely the fibrosed papillary muscles had a good deal to do with the incomplete closure of the mitral leaflets, which accompanied by widening of the ring led to an appreciable degree of mitral insufficiency Concurrently more thrombotic material was deposited in the left subclavian artery so that its lumen was now greatly reduced There was also propagation of the aortic thrombus proximally up to the level of the superior mesenteric artery and distally into both common iliac arteries.

The immediate cause of death was ascribable to a diffuse, acute, purulent and mucopurulent bronchiolitis based on an older chronic bronchitis and obliterative bronchiolitis.

In essence, therefore, diffuse and marked arteriosclerosis and atherosclerosis with thrombosis in this patient gave rise to a series of so-called but incomplete syndromes viz. (1) a Goldblatt kidney with resultant hypertension on the basis of arteriosclerotic involvement of the right renal artery (2) an aortic arch syndrome" with principal involvement of the left subclavian artery which combined with (3) a Leriche syndrome associated with thrombosis of the distal abdominal aorta, led to a clinical complex that simulated coarctation of the arch of the aorta.

Diagnosis Marked diffuse arteriosclerosis and atherosclerosis of the aorta and its branches with (1) marked narrowing and old thrombotic occlusion of the coronary arteries with diffuse myocardial fibrosis (2) marked narrowing and thrombosis of the left subclavian artery (3) marked narrowing of the right renal artery and (4) thrombosis and occlusion of the abdominal aorta and common iliac branches

The hemodynamic effects of digitalis in the normal and diseased heart

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After nearly two centuries the mode of action of digitalis is still not clearly understood. Concepts of its hemodynamic effect have undergone many radical changes since William Withering in 1775 first published an account of his experiences with a new herbal diuretic, foxglove.[1] Attention has shifted successively from the kidneys to the blood vessels and from the blood vessels to the heart. Digitalis has been considered in turn a myocardial depressant and a myocardial stimulant, and the intricacies by which it exerts an effect on the myocardium are still shrouded in mystery. The heated controversy and wide pendulum swings of opinion and concept that have characterized the development of our present knowledge about digitalis and the emergence of new and often divergent experimental data suggest that the final word has not yet been said.

During the first part of the twentieth century the prevailing opinion was that digitalis exerted its beneficial effect as a cardiac sedative. As late as 1926 Harrison and Leonard[2] published a rather elaborate experimental study in the dog which in their opinion supported the concept of digitalis as a myocardial depressant. They believed that the symptoms and signs of congestive heart failure were usually the result of an unbalance between a failing ventricle and a normal ventricle and that digitalis ameliorated the syndrome of congestive heart failure by depressing the function of the good ventricle to the level of the bad one. In the summary of their article they concluded that "digitalis is a cardiac sedative in one sense—it diminishes cardiac output and hence diminishes cardiac work."

Shortly thereafter in 1930 Dock and Tainter,[3] as a result of two brilliantly conceived studies, questioned the sedative action of digitalis and suggested that digitalis preparations act primarily as vasoconstrictors. They postulated that digitalis had an important action on the hepatic veins, constricting them so as to trap blood in the splanchnic vascular bed. They found that in anesthetized dogs the administration of digitalis was followed by a transient rise in blood pressure, a very early drop in central venous pressure and cardiac output, a rise in portal pressure, and an increase in the volume of the liver and spleen. If an Eck fistula was created before the administration of digitalis, the cardiac output and venous pressure rose instead of falling after the administration of digitalis.

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The concept that digitalis acts primarily on the large veins enjoyed considerable acceptance in the late nineteen-thirties and early nineteen forties, reinforced by Katz and his associates[6] and McMichael and Sharpey Schafer who confirmed the findings of Dock and Tainter both in animals and in man. The latter investigators demonstrated that, after the intravenous administration of digoxin cardiac output fell in normal subjects but rose in patients who were in congestive heart failure. They explained this observation by the hypothesis that hearts in failure were on the descending limb of Starling's curve whereas compensated hearts were back on the ascending limb. A reduction in venous inflow to the heart demonstrated in their studies to be associated with a fall in central venous pressure would increase the cardiac output of the failing hearts, but decrease the output of the normal ones in accordance with Starling's law and Starling's curve. They concluded that the apparently inconsistent response to digoxin could be explained if the primary action of the drug was to reduce venous return and atrial filling pressure.

Several other reports were published which suggested that digitalis was detrimental to the normal or nonfailing heart [illegible] Without any experimental verification the concept was promulgated and widely accepted that digitalis increases the "diastolic tone" of the heart and thereby impedes the inflow of blood during diastole

Our knowledge about the effect of digitalis was revolutionized in 1938 when Cattell and Gold[14] demonstrated that digitalis produced a sevenfold increase in the force of systolic contraction of isolated mammalian heart muscle No effect on diastolic tone was observed. This new concept of the hemodynamic effect of digitalis supplanted all previous work but the belief that digitalis was bad for the nonfailing heart persisted among practicing physicians and was perpetuated by standard textbooks of pharmacology and cardiology [illegible]

In 1958 Cotten and Stopp[21] reopened the question of the extracardiac effects of digitalis, particularly in the absence of congestive heart failure. They demonstrated that the administration of ouabain to dogs with normal hearts was followed by an increase in the force of systolic contraction accompanied by an increase in blood pressure and peripheral resistance. There was also a drop in right atrial pressure and a reduction in venous inflow to the heart Because of the reduced venous return cardiac output fell in spite of the increased force of systolic contraction However if by the infusion of blood left atrial pressure was maintained at the levels that existed prior to the administration of ouabain cardiac output rose instead of falling

Recently Rodman Gorczyca and Pastor[22] demonstrated a transient drop in cardiac output in healthy young adults after the intravenous administration of lanatoside C The reduction began within 10 minutes and reached its peak within an hour Two hours after the intravenous administration of 1.2 mg of lanatoside C at which time the myocardial effect was approaching its peak the cardiac output had returned nearly to the control level and the cardiac output response to exercise was normal No reduction in resting or exercise cardiac output was demonstrated in a group of normal adult men who were given a full digitalizing dose of digoxin by mouth over a period of 2 days.

In the light of our present knowledge it appears that digitalis has both cardiac and extracardiac actions and that its pharmacologic activity is the same whether the heart is normal or diseased [illegible] In fact digitalis probably acts upon all types of muscle, voluntary and smooth as well as cardiac.[24] It acts upon arteriolar smooth muscle and produces a rise in peripheral resistance and blood pressure. Its action on the smooth muscle of veins manifests itself primarily by trapping blood in the splanchnic bed and reducing the venous return to the heart In the presence of a nonfailing heart a transient reduction in cardiac output of modest proportions (20 per cent) results. These effects are seen only after intravenous administration are transient and are probably of no clinical significance particularly if the drug is given by the oral route. The action of digitalis on the myocardium produces increased force of systolic contraction In the nonfailing heart no change in cardiac output results from this direct myocardial effect

In the failing heart an increase in cardiac output follows associated with an increased stroke volume and more complete emptying

The chief clinical indication for digitalis is congestive heart failure. Although much attention has been focused on the metabolic and endocrine consequences of circulatory insufficiency and the profound alterations in fluid and electrolyte balance that result from them one should not lose sight of the fact that the underlying cause is failure of the heart as a pump The basic disturbance is a decrease in myocardial contractility the exact cause of which has not been clearly elucidated It has been demonstrated that the production of energy is essentially normal in the failing heart but that a defect exists in the conversion of energy to useful external work. Digitalis apparently is capable of improving myocardial contractility at a cellular level presumably by restoring the ability of cardiac muscle to utilize available energy [11] Although many clinicians have tended to direct their attention to the alleviation of the congestive manifestations that result from cardiac insufficiency by the use of salt restriction diuretics, and aldosterone antagonists, it seems more logical that the primary attack should be an attempt to improve the function of the failing heart directly with digitalis.

The ability of digitalis to improve the function of the failing heart has been amply demonstrated both experimentally and clinically It is most effective in patients with low-output failure and in those whose myocardium is not too severely damaged Unfortunately this observation has led to the erroneous conclusion that it is not effective in high-output failure or when the myocardium is severely damaged In our experience, some clinical improvement may be anticipated in congestive heart failure regardless of etiology cardiac rhythm or the level of cardiac output at which cardiac insufficiency becomes apparent. It has also been suggested that digitalis is ineffectual in conditions associated with mechanical obstruction such as valvular stenosis or constrictive pericarditis. Again it has been our clinical experience that patients with these conditions show relatively less response but do respond and this observation has recently had some experimental confirmation in patients with aortic and mitral stenosis.[17,18]

The importance of the cardiotonic effects of digitalis preparations in the treatment of cardiac arrhythmias is not always fully appreciated. Although the classic pharmacologic effect of digitalis on atrial arrhythmias is supposedly to increase their rate so that atrial fibrillation is perpetuated with an increased atrial rate and atrial flutter converted to fibrillation one frequently observes clinically the termination of both of these arrhythmias and restoration of normal sinus rhythm when digitalization is accomplished This can logically be attributed to the direct improvement in myocardial function by digitalis. We have applied the same principle to the management of frequent premature beats, which are often abolished by digitalization if they are due to underlying myocardial disease. This is particularly important prior to operation or anesthesia during which frequent atrial premature beats may be supplanted by a more serious atrial arrhythmia or ventricular premature beats by ventricular tachycardia We believe that this is a more physiologic approach to the problem than the mere suppression of an irritable focus by quinidine or Pronestyl both of which have a depressant effect on the myocardium

The demonstration that digitalis does not decrease the cardiac output of the nonfailing heart has dispelled the fear that in the past frequently deterred the clinician from digitalizing a doubtful subject preoperatively unless there were overt signs of cardiac failure We would consider it wise to digitalize any patient with cardiac enlargement or a history suggestive of impaired cardiac reserve prior to major surgery Many of these patients may actually be in the early stages of cardiac insufficiency by hemodynamic criteria even though there are none of the peripheral signs of congestive heart failure at the time of examination We believe that it is advisable to digitalize patients slowly by mouth so that the full myocardial effects are achieved rather than depending upon rapid preoperative digitalization except in emergencies. There is an increasing tendency to digitalize all patients prior to

cardiac surgery particularly open-heart surgery[22,23] both as a protection against myocardial failure and to prevent cardiac arrhythmias. It has been shown that there is a loss of digitalization during extra corporeal circulation and some additional digitalis may be necessary after surgical procedures done by open heart techniques. Digitalis has also been shown to protect the heart against the depressant effects of anesthetic agents[23,24] although it is uncertain whether this is of any real clinical significance.

Although it would appear to be unnecessary to digitalize all patients routinely prior to operation the evidence suggests that in older patients, patients with known heart disease, or patients undergoing cardiac surgery it can be accomplished without detriment to the patient and possibly with some prophylactic value.

Summary

Concepts of the hemodynamic action of digitalis have changed greatly during the past 50 years and recent developments suggest that we may reasonably anticipate further evolution of these ideas. Present experimental and clinical observations can best be reconciled with the hypothesis that digitalis exerts a positive inotropic effect on all types of muscle smooth and voluntary as well as cardiac. Indirect cardiac effects result from its action on arterial smooth muscle and on venous smooth muscle primarily of the hepatic veins by altering blood pressure and cardiac inflow. The direct cardiac action results in increased force of systolic contraction with a resultant increase in cardiac output. These effects appear to be the same in normal or diseased hearts, although their external effects in terms of cardiac output may differ.

The prevalent idea that digitalis is detrimental to the nonfailing heart is not compatible with our present knowledge of its pharmacologic properties. In addition to its therapeutic use in cardiac failure of any etiology it can therefore also be used "prophylactically" in patients about to undergo stress such as surgery or delivery if there is any reason to suspect impaired myocardial reserve. It also plays a important role in the prevention and treatment of arrhythmias by virtue of its salutary effect on the functioning of cardiac muscle.

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Evaluation of new single, oblique chest lead for the rapid screening of electrocardiographic abnormalities in large populations

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Finding significant electrocardiographic abnormalities often makes it possible to recognize heart disease which is undetectable by other techniques, such as chest x ray examination and physical examination of the patient Simple rapid and reliable electrocardiographic screening techniques are needed for surveys of mass population because the multiple-lead electrocardiogram is generally too time consuming and expensive for large-scale screening We have studied a single oblique electrocardiographic lead which makes it possible to detect a high percentage of significant electrocardiographic abnormalities in a large number of subjects with minimum effort and maximum convenience. Application of the electrodes and recording the single lead electrocardiogram required less than 2 minutes for each subject

Methods

The single oblique lead was obtained by recording the potential differences between an electrode positioned just below the clavicle to the right of the sternum and an electrode placed at the left posterior axillary line two to three fingerbreadths below the tip of the scapula This lead might be presumed to be approximately collinear with the mean electrical axis of P and QRS and therefore would have impressed on it horizontal vertical and sagittal components of the electrocardiogram Thus, it should be capable of detecting abnormalities in any plane.† This lead was recorded by placing the right arm lead wire on the anterior chest electrode and the left arm lead wire on the back electrode with the lead selector on Lead I Variations up to 2 inches in any direction in actual placement of the electrodes did not alter appreciably the configuration of the tracing A copper electrode connected to ground through the right leg electrode was grasped by the subject. A halter with the electrodes attached allowed the electrodes to be slipped into position easily without the subject's being required to disrobe (Fig 1) Good contact without

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Appraisal and reappraisal of cardiac therapy

Mebutamate

Antihypertensive or tranquilizer?

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Mebutamate is being promoted as a mild antihypertensive agent with a central action No direct action on the blood vessels or ganglia is claimed Chemically it is a close relative of meprobamate the only difference being an additional methyl group on the propyl side chain It seems reasonable, then to assume that mebutamate would have pharmacologic properties similar to its parent substance meprobamate. In other words, it should have a sedative effect. Early reports in the literature indicated that mebutamate had only a mild tranquilizing action and that its main effect was antihypertensive Recent reports, on the other hand show that when an antihypertensive effect with mebutamate alone is achieved drowsiness as a side effect is noted in nearly every case The data in one recent report indicate that mebutamate has actually a greater sedative effect than does meprobamate in comparable doses.

Several double-blind studies in which mebutamate is compared with a placebo are now available The drug is given in doses of 300 mg either three or four times a day All reports but one consist of tabular comparisons of blood pressure recordings, without statistical analysis. The only paper in which a careful statistical evaluation of the data was made shows no significant difference between mebutamate and a placebo or mebutamate and meprobamate as far as effects on hypertension are concerned The well known effects of a sedative on mild hypertension of neurogenic origin are largely disregarded by most nvestigators.

Since only a mild antihypertensive effect is claimed for mebutamate t follows naturally that attempts to enhance ts effect by combination with well-established antihypertensive agents would be tried Thus, combinations with on of the thi azides have been made and studies indicate an increase in antihypertensive effect, as would be expected. The one report in which the data were nalyzed statistically showed that the add tion of mebutamate did not increase the antihypertensive effect of hydrochlorothiazide.

Thus from the evidence so far ava l able t would appear that mebutamate is primarily sedative or tranquilizer and that y effect it may have on hypertension s due to sedation and not to a y specific action directed primarily to the reduction n blood pressure alone

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[illegible] and trade names of drugs mebutamate—[illegible]; meprobamate—Miltown, Equanil.

Annotations

Hypotension and shock syndrome complicating staphylococcal pneumonia

Hypotension and shock syndrome are now well recognized as complications of bacterial infections. Reports to date, however, have been concerned predominantly with surgical conditions complicated by bacteremia. *Escherichia coli* has been the most commonly described responsible organism and is believed to be particularly prevalent in genitourinary instrumentation or surgery and certain obstetrical or gynecological conditions. By contrast, only occasional cases of shock syndrome induced by *Staphylococcus aureus* have been included among larger groups of case reports dealing with this condition. The lungs have been a very infrequently described source of primary infection.

A recent report from New Zealand of staphylococcal pneumonia complicated by hypotension and oliguria (or anuria) is, therefore, of universal interest. In a consecutive series of 48 patients with radiologically and bacteriologically (coagulase-positive) proved staphylococcal pneumonia there were 15 who suffered significant hypotension and impairment of renal function. Of these 10 died despite relatively prompt and accurate diagnosis, with subsequent energetic antibiotic and resuscitative therapy. In those in whom staphylococcal pneumonia was not complicated by hypotension and shock syndrome the mortality was 6 per cent. Nonstaphylococcal pneumonia during the same period was associated with a mortality of 10 per cent. There were 2 patients with nonstaphylococcal pneumonia who developed hypotension and severe oliguria. In one, a pure culture of Pneumococcus was obtained in life and after death, whereas in the other, coagulase-negative *Staphylococcus aureus* was cultured consistently from the sputum.

Nine of the 10 patients who died were seen at necropsy and all had extensive pneumonia. In each instance, adrenal tissue was normal. Despite severe hypotension no lesions were demonstrable either macroscopically or microscopically in the myocardium. In 6 patients the kidneys were strikingly pale. Renal tubular necrosis was present in 2 of these and less extensive tubular changes were evident in another. Acute renal tubular necrosis has been noted previously complicating staphylococcal pneumonia. The mechanism of production is probably complex, and relevant factors include anoxia, direct effect of alpha-toxin upon renal parenchyma, impaired renal blood flow secondary to hypotension, vasomotor disturbances associated with shock, and, even possibly, side effects from vasoconstrictor drugs used therapeutically.

It is clear that very real prognostic significance can be placed upon the occurrence of hypotension and impairment of renal function in pneumonia. Kellaway and Le Grice found that in 50 per cent of the patients who died with staphylococcal pneumonia complicated by hypotension and shock syndrome death occurred within 48 hours of their admission to hospital. Two more patients died within 72 hours, and another 2 died within 72 hours of a recrudescence of infection, 2 weeks after stopping antibiotic therapy. The mortality among patients with hypotension and oliguria was 67 per cent. Experience has been similar in shock syndrome induced by Gram-negative cocci. Mortality rates of 40 to 65 per cent have been reported, whereas Spink has noted that when *Escherichia coli* shock syndrome is complicated by renal failure the death rate exceeds 70 per cent.

In dealing with this problem therapeutically prompt diagnosis is clearly essential. The most valuable diagnostic aid is direct examination of a Gram-stained sputum smear. When clumps of Gram-positive cocci are absent, a diagnosis of staphylococcal pneumonia can generally be disregarded. When no sputum can be obtained, staphylococcal infection can only be suspected by clinical assessment and careful study of chest x-ray films. Once diagnosis is suspected with some degree of certainty the choice of immediate antibiotic therapy depends logically upon knowledge of local antibiotic sensitivities and resistances. With this in mind suitable intravenous combinations can be commenced pending results of sputum culture.

Management of hypotension is open to debate. Even though risks of corticosteroid therapy in the presence of staphylococcal infections have been stressed, the administration of hydrocortisone is usually advocated when hypotension and shock syndrome occur as a complication. It is claimed that, even though endogenous cortisone excretion is usually normal, or greater than normal, in shock syndrome due to infection, the use of exogenous hydrocortisone can help by a pharmacologic rather than a physiologic action. In seeking guidance for the use of vasoconstrictor agents, there appears to be little relevant published experimental data with staphylococcal exotoxins, except for physiologic observations upon the site of action by Thal and

Egner From nimal experiments using *Escherichia coli* endotoxin,[8] however it ppears that the protective action of vasopressor agents, adrenergic blocking substances, nd corticosteroids depends largely upon the degree of hypotension present, its duration, nd whether the "protective drugs are given before, during or after administration of toxin. There is still sufficient variation in result reported by ind vidual workers t leave doubt as to how efficacious vasopressor agents are likely t prove and at what stage their use can be actually harmf l. It certainly ppears probable that they should be administered sooner rather than later and certainly before shock can proceed to the ir reversible phase. Once this has occurred, their use may well encourage hypotension and hasten death.

Some patients with severe staphylococcal pneumonia who develop shock syndrome are relatively young. In selected cases it is possible that intensive resuscitative measures, including hypothermia, extracorporeal circulation, and use of an artificial kidney may prove to be most rewarding. If this is to be contemplated seriously however further detailed observations pon relative physiology nd action of vasopressor drugs in exotoxin-induced shock syndrome is urgently indicated.

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Selective ischemia in diving man

Circulatory events associated wi h compensated shock ha received much recen tention Protective reactions ha e been described as massive vasoconstriction of renal, mesenteric and peripheral circulations producing diversion of blood to the heart nd brain t maintained pressure Thus, the total circula ion is reduced to the minimum con sistent with adequate perfusion of the organs most ital for survival

These adj stments bear striking resemblance to the cardiovascular events which occur in di ing animals. The general fea ures of his response ha been well established[1] nd re known to include vasoconstriction in he periphery and iscera, maintenance of ystemic blood pressure and supply he brain nd heart The accompanying pronounced bradycardia ppears to be consequence of the widespread ischemia. For the diving animal his reaction operates to conserve the otherwise inadequate stores of oxygen for vital organs of poor anaerobic capability such as the brain and heart The existence of this circulatory bypass rests upon several pieces of evidence Heated wire flow meter techniques have been used to demonstrate hat he flow of blood in skeletal muscle decreased, whereas brain perfusion remained nchanged or increased. The renal and mesenteric circulation are drastically restricted. Furthermore, the

of blood the muscles of most diving and nondiving animals is so reduced that lactate produced in large quantities by vigorous activity during the dive, does not appear in the general circulation until the flushing out which occurs immediately upon recovery. There is good evidence that the ischemic organs subsist on greatly reduced energy metabolism. Even fishes when taken out of water show these reactions.

Only recently has a search been made for similar reactions in diving man. Bradycardia is well established and is often complicated by various cardiac arrhythmias. Flushing out of lactate has also been found after dives and reduced flow of blood in the finger has been observed during breath-holding.

Fetal bradycardia and flush-out of blood lactate in recovery after birth strongly suggest that a mechanism similar to diving may operate during birth asphyxia.

The present study was undertaken in search for ischemic reactions in skeletal muscle by measurements of blood flow in the limb during diving in man. Five young adult male subjects were used in experiments in which heart rate and blood flow in the calf were measured simultaneously in the supine position during simple breath-holding and during diving which consisted of immersion of the face in water. Blood flow was measured by venous occlusion plethysmography using the Whitney strain-gauge plethysmograph. All experiments were repeated at least three times. The breath-holding or dive period lasted from 40 to 60 seconds. All 5 subjects experienced bradycardia during the dives. The flow of blood in the limb measured at 30 seconds after the dive started was reduced in every instance. For each of the 5 subjects the flow was decreased to an average of 80, 68, 35, 30 and 14 per cent, respectively, of the control pre-dive values. The blood flow and heart rate decreased more during immersion of the face than during simple breath-holding, and was accentuated when performed in expiratory position. In one subject with normal blood flow before and after the dive it was impossible to detect any flow in three of five dives.

It appears therefore, that man and animals alike meet the stress of apneic diving through selective ischemia. This is a very widespread and basic asphyxial defense mechanism found throughout the vertebrates, from mammals to fishes. In man it seems developed already at birth and we find the response operating from simple breath holding to shock. The common feature in all of these cases is that the organism "turns into a heart lung-brain preparation" to quote a recent statement by Dr. D. D. Van Slyke.

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Psychogenic retention of water

Recent reports by Hill and associates, Thorn, and others on the subject of "idiopathic pedal edema" in psychologically disturbed females has generated some interest in the study of psychological factors in the production of water retention states. Although this syndrome appears to be a distinct entity and apparently unrelated to demonstratable cardiac, renal, or hepatic disease, one may speculate, on the basis of evidence presented below, that it may be reflective of an exaggeration of a normal phenomenon, the retention of water during a psychologically disturbed state. Recent psychosomatic research, documented in the areas of functional hypoglycemia and hypersecreting ulcer in relationship to uropepsin level, indicates that many of the so-called psychosomatic disease entities are probably exaggerations of normal physiologic events. Thus, the possibility that a psychological state may influence significantly water balance may have implications for refractory edematous states, the precipi-

tation of cardiac failure with psychological disturbance, as well such well-defined entities as cyclical edema.

Hoff and Wermer and Heilig and Hoff in 1925 reported significant hypnotic influences on both the retention and diuresis of water in man. Marx, in 1931 was able to produce (in 1 out of 4 dogs) diuretic effect conditioned not only to specific musical tone, but to the experimental environment without water load. Rydin and Verney in 1938 reported an inhibition of water diuresis after water load dogs by either stimulation of afferent pain fibers or loud noises. Eagle in similar experiment, also showed conditioned inhibition of water diuresis after water load. Wolf[?] in 1943 and Kelsall,[?] in 1949 demonstrated the inhibition of water diuresis after water load in man by an ischemic muscle pain. Wolf showed associated changes in the renal blood flow glomerular filtration rate and filtration fraction. Abrahams and Pickford[?] were able to demonstrate conditioned antidiuresis after several injections of posterior pituitary extract by saline injection in dogs. Abelson and associates,[?] from Russia, showed that classroom demonstration situation facilitated water diuresis in some dogs and inhibited water diuresis in others, depending upon the personality of the dog. They likewise demonstrated that decortication produces decreased flow of urine and renal degeneration changes on the side of the brain lesion. They deduced that the higher central nervous system influences significantly the management of water by the kidney. Verney[?] demonstrated the effect of emotional stress and preexercise conditioning on the inhibition of urine flow in dogs. In similar kind of conditioning experiment in dogs, Dykman and associates have recently shown rather dramatically in 1 out of the 2 dogs studied that inhibition of the flow of urine is component of the conditional defense reaction. However they failed to demonstrate that it was tied to specific stimulus. Toth an interesting type of learning situation in man showed that, when patient ingested water in prone position 17 times consecutively, this resulted in diuresis in subsequent trials without water load whenever he got in the experimental situation and supine. Schottstaedt and associates,[?] interesting series of longitudinal studies on 5 human subjects, in which the subjects were examined upon their psychological state numerous times during the day and continuously collect their urine demonstrated that the diet associated with the anticipation of successful action resulted in diuresis of water and sodium where the emotional disequilibrium associated with the conception or fear of failure before act was associated with retention of fluids and electrolytes. Wittig[?] has recently demonstrated that in man hypnotic suggestion of thirst work resulted in increased retention of water and that the changes which occurred in the filtration fraction and minute volume (an increase) were identical to those which occurred in work. Mandell,[?] employing psychological tests, clinical psychiatric interviews and water load study the dependent variables of clearance of free water and of creatinine studied 10 psychiatric patients the time of their admission to the hospital.

patients were without any renal, cardiac or hepatic disease. They were studied again 1 month later. They were not on medication and were followed during the interim with clinical psychiatric interviews. The 7 patients who showed appreciable clinical improvement, as well as improvement in the psychological testing demonstrated on retest an increase in the clearance of creatinine and free water the 3 who became clinically worse demonstrated decrease in creatinine and free water clearance.

Without discussing the multiple intervening variables that could be held accountable for the influence of the psychological state on water balance (17-OH corticoids, ADH renal vessels etc.), it appears that the evidence points toward the psychological state as significant variable in patients with water retention. Rizzo and associates[?] have demonstrated the remission of cyclic idiopathic pedal edema in patient treated only with psychotherapy. It would seem that this line of evidence point toward at least some attention on the doctor part to the state of the interpersonal relationship as well as the patient psychological status in cases in which organic manipulation of the water balance in patients has proved to be of limited value. As noted above it would appear that this has implications not only for specific entity of idiopathic cyclic edema but for any of the multiply caused edematous states. Perhaps one suggested and definite kind of manipulation of the psychological state might be the use of tranquilizers. There has been recent report[?] that chlorpromazine increased the excretion of water sodium and potassium in patients with congestive heart failure due to cor pulmonale, although it failed to do so in patient with congestive heart failure due to hypertension or aortic insufficiency. Miles and De Wardener[?] report osmotic diuresis after discussion of the patient illness, more marked in hypertensive than in normotensive patients.

Thus the psychological state of patient appears to be another manipulable variable in the treatment of water retention states.

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Unusual manifestations of pheochromocytoma

Patients with pheochromocytoma classically present with attacks of hypertension associated with pallor sweating tachycardia, and vomiting Many patients do not present this characteristic pattern, so that diagnosis may be difficult. In a recent paper devoted to unusual manifestation 6 cases were described In 3 of these the symptoms suggested primary renal disease whereas in the others initial diagnoses of gallstone colic, cerebral tumor and toxemia of pregnancy were made.

In 2 patients, episodes of oliguria albuminuria, and a raised blood urea were associated with the hypertensive crises. In one persistent fever was also present, and an erroneous diagnosis of pyelonephritis was at first made. In both patients a deep red facial flush developed during, and persisted for several days after the hypertensive crises the deep red parboiled hue of the face and neck were in striking contrast with the cadaveric appearance of the extremities, which were cold cyanosed, and moist. In both patients the hemoglobin level rose to from 130 to 140 per cent during the hypertensive crisis, and persisted for seven days before returning to normal. The cause of this facial flushing was not clear but, as suggested, it might have been due to the effect of the transient increase in blood flow in the skin which is known experimentally to occur at the end of an infusion of noradrenaline in association with the high hemoglobin level which in itself may have resulted from the ability of noradrenaline to cause a contraction of the plasma volume and an increase in the venous hematocrit

The episodes of renal failure were attributed to the effect of noradrenaline and adrenaline on kidney function. In pheochromocytoma reduction in renal plasma flow and urea clearance[2] has been demonstrated during attacks of hypertension whereas experiment in dogs[3] have shown that infusion of sufficient noradrenaline may lead to renal shut down.

The third patient a 22 year-old housewife, developed severe hypertension during the early months of the fifth pregnancy two previous pregnancies had been similarly complicated. The pregnancy was terminated by abdominal hysterotomy after which an unexplained postoperative collapse occurred, with a fall in systolic pressure to 60 mm. Hg This collapse after anesthesia raised the suspicion of pheochromocytoma, which was subsequently demonstrated. It was of interest that 2 years previously investigations had been carried out to determine the cause of the hypertension

and at that time the catecholamine excretion was within normal limits in four 24-hour specimens examined. A past history of acute nephritis in childhood had led to the erroneous diagnosis of latent glomerulonephritis.

The fourth patient, a 48-year-old woman, presented with attacks of abdominal pain, vomiting and headache, of several months duration. On admission to hospital she was pale, the blood pressure was 120/80 mm. Hg there was tenderness in the right hypochondrium, and a cholecystogram revealed gallstones. After cholecystectomy the attacks persisted and during one the blood pressure rose to 220/110 mm. Hg and led to the correct diagnosis of pheochromocytoma. Pheochromocytoma has previously been mistaken for an abdominal catastrophy

The fifth patient, a 15-year-old boy developed attacks of frontal headache, worse on the right side. The attacks were associated with vomiting, and on one occasion two convulsions on the left side occurred, with incontinence of urine. These features, together with the finding of gross papilledema, led to a diagnosis of cerebral tumor despite the presence of severe hypertension, and it was only after investigations had failed to confirm the presence of a tumor that the correct diagnosis was made.

The final patient was a 29-year-old woman who in the fourth month of the fourth pregnancy developed severe headache, sweating and blurring of vision. The blood pressure had risen to 180/140 mm. Hg from normal levels, and Grade IV retinopathy was present. A diagnosis of toxemia was made, but the presence of sweating and wide fluctuations in blood pressure after treatment with hypotensive agents led to the diagnosis of pheochromocytoma.

In reviewing the histories of these cases, the authors stressed the importance of sweating as a diagnostic feature It was present in all patients and in several was the symptom which eventually led to the correct diagnosis. The value of the estimation of 3-methoxy-4-hydroxy-mandelic acid (vanillmandelic acid) as a diagnostic procedure was emphasized. The danger of attempting to localize the tumor by perirenal insufflation was stressed. In 2 cases this procedure had led to dangerous hypertensive crises.

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Book reviews

PRACTICAL ELECTROCARDIOGRAPHY. By Henry J. L. Marriott, M.D., Director of Medical Education and Director of the Cardiology Center, Tampa General Hospital, Tampa, Fla. Ed. 3. Baltimore, 1962, The Williams & Wilkins Company. 274 pages. Price $3.50.

The new edi ion of this practical ma ual on clinical lectro rdiogr phy continues t provide n excellent text for n introductory ourse in bedside electrocardiographic terpretation.

The simplicity of org ization of the previou ed tions is retained but significa t revisions are evident in the chapters that deal with ventricular hypertrophy, intra entricular block, A-V dissociation, and congenital heart disease. New t this edition is welcomed word about vectors. The author tyle remains nformal, adding both to the appeal nd readability of the book.

The uthor tilizes the standard pattern riteria for the diagnosis of the more common lectrocardiographic abnormalities and clearly defines nd outlines these criteria for the reader. The text is liberally ugmented with representative electrocardiograms adjacent to the pertinent text. A group of unknow electrocardiograms is lso presented for review purposes.

Although devoid of lectrophysiologic principles and generally oiding the troubled sea of ectors axes nd gradient the book readily f lfills the uthor objective in presenting manual of practical principles and criteria for lectrocardiographic interpretation.

The book ca be recommended as text for introductory course in practical pattern interpretation. I is of limited value to the experienced electrocardiographer.

HEART-LUNG BYPASS. P INCIPLES AND TECHNIQUES OF EXTRACORPOREAL CIRCUL TION. By Pierre M. Galletti, M.D., Ph. D., Assista t Professor of Physiology, nd Gerhard A. Brecher, M.D., Ph.D., Professor nd Chairma , Department of Physiology, Division of Basic Health Sciences, Schools of Medicine, Dentistry, nd Nursing, Emory Un ersity, Atla ta, Ga. New York, 1962, Grune & Stratton, Inc. 391 pages. Pric $14.50.

This book ill be seful to yone without prior experience ho wants to get detailed information in regard to the principles nd techniques of extracorporeal circulation. I addition the uthors hav performed real service for those who re acti ely engaged i research or the clinical application of extracorporeal circulation by compiling the extensive bibliography on which the book is based. The summarizing paragraph t the conclusion of ea h chapter are particularly usef l, in that the sense of the preceding chapter is usually delineated without ll the disturbing clutter of bibliographical reference.

Some sense of dissatisfaction is felt on reading this book, since little attempt is made t simplify or correlat the mass of information that is presented. This is probably not yet the time to do this, and the uthors were perhaps wise not to attempt extensive interpretations. The historical references serve a worth-while purpose in many instances but they too often tend to ll the pages without contributing much more than priority recognition.

It becomes obvious in reading the chapter on the effect of perfusion on organs that very little has been done to discover why there are limitations on the duration of perfusion. The changes induced by whole-body and partial perfusion are well described.

This olume is valuable for the clear definitions of terminology nd for its extensive bibliography. It is depressing to see the word "extracorporeal" misspelled on the hard cover of the volume.

BUERGER'S DISEASE (A Follow-Up Study of World W II Army Cases). By Michael E. DeBakey, M.D., Chairman, Department of Surgery, Baylor University, nd Bernard M. Cohen, Ph.D., Statistician, Follow Up Agency, National Academy of Sciences, Washington, D.C. Springfield, Ill., 1962, Charles C Thomas, Publisher. 143 pages. Price $8.50.

Thi book is epidemiological tudy of the United States Armed Forces experience with Buerger disease during World War II and as such it is q ite complete, comprehensive, tatistically sophisticated, and informative. It suffers from inherent difficulties, such as lack of resolution of certain fundamental questions raised by the stud a well a by other investigators of the disease. These shortcomings ha e been poi ted out by the authors but the fact that they have been recognized does not render the tudy itself ny more informative with reference t such questions. It has been pointed out for example that differentiation between rteriosclerotic nd thromboangiitic lesion ca not alway be made clinically or even pathologically. Since there is also an entity called "thromboatherosclerosis" it is clear that exact diagnosis is difficult if not impossible especially because thrombose l arteries are frequently asymptomatic.

The evaluation of Army and Veterans Administration records moreover is retrospective, lthough analysis of questionnaire sent out t these patients is lso presented. Such study therefore suffers lso from lack of direct contact bet een the physicians evaluating the material and the patients.

Some of the fundamental questions which are left unanswered are:

1. How specific is the pathologic diagnosis in this disease?

2. What is the difference bet een thrombosis within rteriosclerotic vessel and thrombosis within essel which is not arteriosclerotic?

3. Can Buerger disease occur on arteriosclerotic base In other words, are we not really dealing with t entities, one of which is thrombosis within arteries and also within veins, and the other of which is thrombosis withi a vessel which is arteriosclerotic?

4 Also what is the relationship of etiological factors such as moking to the complex? This question has been answered in part in this book, but, again, the answer ca be accepted as only fragmentary and inconclusiv

Certain points however have been clarified to some extent. For example it was shown that neither mpathectomy nor amputation influenced mortality in the disease. Nothing is mentioned however bout the effect of these procedures on morbidity or of the effect of sympathectomy on the necessity for amputation in these extremities. Also it is clear from this tudy that the most important cause of death in Buerger disease is cardiovascular and chiefly cardiac and that mortality in general is not so high as some authors would have ticipated. The tudy also indicates again that the disease occurs chiefly in people who smoke N clear-cut relationship however could be demonstrated between cessation of smoking and amelioration of symptoms or decrease the necessity for operation.

The book is not meant t be general treatise on Buerger disease nd would be of limited interest to those concerned with pathogenesis or involved in general management of the disease. It is, however contribution to knowledge in this area and should make valuable addition to the bookshelf of the specialist in the field of vascular diseases.

Application of Computers in Cardiovascular Disease (Proceedings of Symposium held Feb. 27 and 28, 1962 in Philadelphia, sponsored by The Heart Association of Southeastern Pennsylvania nd the Pennsylvania Department of Health). Edited by John H Moyer M D Professor and Chairman, Department of Medicine Hahnemann Medical College and Hospital, Philadelphia, Pa. New York 1962 The American Heart Association, Inc. (Monograph No 5), 650 pages. Price $2 50.

The monograph consists of 25 articles from 42 contributors I 14 of the articles there is no author participation by doctors of medicine. A distribution of this kind is certainly to be expected. The great number of physicians who are now engaged research probes of cardiovascular disease medical education, and administra ion are i no position to communicate formally with the h ghly skilled nonphysician scientists who are in step with an exploding domain of electronic magic. These rticles predict exciting oncourse collision of medical-center nd hospital physicians with computer scientists. The dvantage to be gained by ll will eventually far exceed the domain of ideas and examples which are presented in this monograph

The articles indicate that electronic computers obey operative demands of the multivalent hu man computer t speed and t an accuracy which is lmost beyond everyday comprehension Economically computer center must in time repay far beyond its cost of installation nd operation.

A most comprehensive article is that by Dr O H Schmitt. H indicates that much of the importa t physiologic data may be frequently represented by low change of oltage with respect t time nd that modern recording methods (frequency modulated on magnetic tape) cannot be directly subjected to analysis with the powerful high-speed modern digital computer A so-called analogue-to-digital converter is required as an intermediate step.

Dr Schmitt indicates that his laboratory is working on new method of "bivalent tape ecording of the physiologic electrical equivalents. This type of recording he states, may be retrieved in its original (nalogue or graphic) form for analogue computers and also may be at once compatible as an input source to the digital computer

Some of the technically interesting articles are contributed by R. F Rushmer on left ventricular pump function by G R. Meneely and associates on total body electrolyte measurement by D A. Brody on tensor-electrocardiography and by D S. Gerbarg and associates on heart sound nalysis.

Several of the articles properly emphasize that electronic computers are subordinate to the multivalent *human mental computer* The latter must first develop sound data-gathering method and then an ppropriat electronic computer instructional program. The outcome from the lectronic computers will be no better tha these systems, and unless the problem is pproached very gradually and thoroughly maring and lmost unbelievable errors will result. Nevertheless, computer methods ca be used to great advantage in the general areas of medical diagnosis therapeutic accuracy and in epidemiological tudies and administrative techniques. E entually the computer laboratory may be expected t dictate much of the exciting medical-center and hospital procedure

Announcements

During the Fourth International Congress of Cardiology held in Mexico City from October 7 to 13, 1962 the results of the competition for the RECORDATI INTERNATIONAL PRIZE FOR CARDIOLOGY were announced. The prize amounted to $2,000 U.S.

Said competition was open to physicians of any nationality who presented an unpublished paper on a subject in the field of cardiology. The prize was awarded to the Polish physician Dr. Tadeusz Petelenz, author of the paper "Extra-Coronary Arteries of Human Myocardium."

The panel of judges was composed of five eminent cardiologists: Prof. Condorelli, of Rome, Prof. Chávez, of Mexico City, Prof. Décourt of São Paulo, Prof. Lenègre of Paris, and Prof. Katz, of Chicago.

During the official banquet for the scientists who attended the Congress, Prof. Condorelli, head of the panel of judges in the presence of Dr. Arrigo Recordati, managing director of the Recordati Pharmaceutical Laboratories, handed over the Prize to the Polish chargé d'affaires in Mexico.

THE IV LUSO-SPANISH CONGRESS OF CARDIOLOGY will be held at the Faculty of Medicine, Porto, Portugal from April 17 to 20, 1963. The Congress is being conducted under the auspices of the Portuguese Society of Cardiology and the Spanish Society of Cardiology.

Registration forms and additional information in regard to the Congress may be obtained from the Secretário, J. Pereira Leite, Serviço de Patologia Médica, Faculdade de Medicina do Porto, Hospital Escolar de S. João, Porto, Portugal.

AN INTERNATIONAL CONFERENCE ON RENAL HYPERTENSION sponsored by the Division of Urology and the Department of Medicine, Ohio State University College of Medicine will be held on July 12 and 13, 1963 in Columbus, Ohio.

The speakers and their subjects are as follows: Dr. I. H. Page, Cleveland Clinic, Cleveland, Ohio—History of Subject, and Natural History of the Disease; Dr. W. S. Peart, St. Mary's Hospital, London, England—Etiology; Dr. L. J. McCormack, Cleveland Clinic, Cleveland, Ohio—Classification of Pathologic Lesions; Dr. J. Genest, Hotel-Dieu, Montreal, Canada—Differential Diagnosis; Dr. O. M. Helmer, Lilly Laboratory, Indianapolis, Indiana—Bioassays of Renin and Renin Substrates; Dr. A. Rapoport, Toronto University, Toronto, Canada—Diagnostic Individual Renal Function Test; Dr. E. F. Poutasse, Cleveland Clinic, Cleveland, Ohio—Urographic and Aortographic Diagnostic Procedures; Dr. C. C. Winter, Ohio State University College of Medicine, Columbus, Ohio—Selection of Patients for Surgery and Prediction of Outcome; Dr. P. T. DeCamp, Ochsner Clinic, New Orleans, Louisiana—Surgical Treatment; Dr. M. E. DeBakey, Baylor University College of Medicine, Houston, Texas—Surgical Techniques; and Dr. I. H. Page—Summary of Presentations.

There will be panel discussions, a motion picture, exhibits, demonstrations of tests, a social hour and banquet.

The registration fee is $30. For information and registration, contact: John A. Prior, M.D., The Center for Postgraduate Medical Education, Ohio State University College of Medicine, 113 Hamilton Hall, 1645 Neil Avenue, Columbus 10, Ohio.

The University of Kentucky Medical Center wishes to announce a course in RECENT ADVANCES IN CLINICAL CARDIOLOGY to be given at the College of Medicine in Lexington, Ky., on May 9, 10 and 11, 1963. This will be a 2½-day course with exercises in electrocardiography and phonocardiography, lectures, presentation of problem cases, panel discussions and clinical pathologic conferences. The registrants will participate in all phases of the program.

The fee is $15 for the 2½-day course.

Information and registration may be obtained by writing to Nicholas J. Pisacano, M.D., Director, Continuation Medical Education, University of Kentucky Medical Center, Lexington, Ky.

THE SECOND HUNGARIAN CONGRESS OF INTERNAL MEDICINE, with international participation, will be held from Sept. 30, 1963 through Oct. 5, 1963 in Budapest, Hungary.

The main theme of the Congress will be Cardiology, with the following topics to be discussed: congenital heart disease in adults, rheumatic valvular disease, rare heart diseases, coronary disease and methods of cardiological investigation.

Address correspondence to: Professor Dr. G. Gottsegen, President of the Congress, Nagyvárad tér 1, Budapest IX, Hungary.

THE FIRST INTERNATIONAL TELEMETERING CONFERENCE will be held Sept. 24-27, 1963. The Technical Program will be at Headquarters, Institution of Electrical Engineers, Savoy Place, London, England, and the International Exhibit will be at the New London Hilton Hotel, London. The sponsors are A.I.E.E., A.R.S., I.A.S., I.R.E., I.S.A., *I.E.E. (U.K.), and I.R.E. (U.K.).*

Contact: Allan P. Gruer, Chairman, 7530 Sandia Corporation, Albuquerque, N. M.

THE 1963 NATIONAL TELEMETERING CONFERENCE will be held May 20-22, 1963, at the Hilton Hotel, Albuquerque, N. M. The sponsors are A.I.E.E., A.R.S., I.A.S., I.R.E., and I.S.A.

Contact: A. E. Beatz, Chairman, 7113 Sandia Corporation, Box 5800, Albuquerque, N. M.



Fig. 1. Electrodes and their support for recording the oblique lead. *Left*. Plastic electrode support and electrodes. Additionally 2 copper electrodes for ground connection are shown. *Right*. Plastic halter and electrodes positioned on patient who is grasping the ground connector. One electrode is at the posterior axillary line below the tip of the left scapula, the other at the right parasternal line below the clavicle. (The halter was fabricated by M. B. Burk, Oklahoma State Department of Health.)

prior preparation of the skin was obtained by using electrodes of the liquid contact type. Tracings were taken at 50 or 75 mm speed at normal sensitivity. Generally, 4 to 6 complexes were recorded. Tracings were obtained with the subject in the sitting position and muscle tremor did not prove to be a problem. There was no noticeable effect on the tracing produced by maximal respiratory excursions of the thorax. All subjects had standard multiple-lead electrocardiograms recorded for comparison with the oblique lead.

Normal values for the oblique lead were established from electrocardiograms obtained from 100 adult subjects whose standard multiple-lead electrocardiograms were interpreted as normal. Electrocardiographic surveys using the oblique lead were conducted as follows: (1) an initial survey of 352 patients was made at the Oklahoma City Veterans Administration Hospital; (2) four small groups (76 employees of the Oklahoma State Department of Health, 143 inmates of the Oklahoma State Penitentiary, 19 National Guardsmen, and 62 members of an elder citizens club) totaling 300 subjects were surveyed; (3) finally, 1,286 patients at Central State Hospital, Norman, Oklahoma, were screened (however, in only 346 of these was the standard electrocardiogram available for comparison).

Thus, a single and standard electrocardiogram were available for comparison in a total of 996 subjects. The single-lead and standard-lead electrocardiograms were interpreted independently. In Groups 1 and 2, separate observations of the single lead were made by 2 of us for interindividual comparison with the standard electrocardiogram.

In the Central State Hospital survey the standard hospital electrocardiogram obtained within 5 years of the survey was not repeated unless it was in disagreement with the single-lead electrocardiogram (48 cases) or unless the routine electrocardio-

*Manufactured by Alloyd Engineering Laboratories, Inc., Mound View Road, Verona, Wis.

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Editorial

Coronary interarteriolar anastomoses

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As a cause of death and of invalidism heart disease now much exceeds in importance any other medical problem at least in the Western world. Of those patients who develop heart disease the great majority are suffering from myocardial ischemia which may be caused by either an increased demand as in hypertrophy or valvular disease or a decreased supply of which the most important cause is atherosclerotic narrowing of the coronary arteries and/or their ostia. In fact the World Health Organization Expert Committee on cardiovascular diseases and hypertension define the term ischemic heart disease as being the cardiac disability acute and chronic arising from reduction or arrest of blood supply to the myocardium in association with disease processes in the coronary arterial system "[1] It is this coronary heart disease which has now become so grave a medical problem likened by Paul White[2] to a devastating epidemic

Unfortunately unlike the situation in the great epidemics of infectious diseases, we have no method of simple protection against myocardial ischemia no vaccination or antitoxin In spite of the expenditure of vast sums of money and vast amounts of work on the subject, we still know remarkably little about the problem and its cause. In fact there is a most disturbing lack of knowledge concerning some of the most fundamental aspects of the structure and pathophysiology of the heart. Recent technical achievements have enabled us to carry out on living hearts hitherto undreamed-of experiments yet this would seem to have diverted attention from more prosaic but more important basic studies. Indeed there is a danger that the conclusions drawn from some of the more technical work may come to resemble a great inverted pyramid of theory based on a gravely unsubstantial basis of proved fact. This is strikingly illustrated in the field of what is surely the simplest of all facets of the problem namely the anatomy of the coronary arteries. It is only a few years ago since first Brink[3] and then Singer[4] showed that in addition to the well-recognized two primary divisions of the left coronary artery i.e the left circumflex branch and the left anterior descending branch a third main primary division is present in over 21 per cent of human beings. This third

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primary division takes origin from the common trunk midway between the circumflex and the anterior descending branches; usually it is smaller than the other two main branches, although on occasion it may be the biggest of the three branches. Another variant of the normal anatomy is that on the right side the conus branch has a separate orifice from the main artery in a large majority of individuals. These are two common variations of the normal anatomy, yet they are not mentioned in several textbooks which deal with this subject. In 1938 Schlesinger[6] drew attention to the infinite variety of the coronary arterial patterns and likened them to fingerprints in their individuality. Clearly, a full understanding of the major variants will only be attained by the detailed study of many hundreds of coronary artery systems; at present no such information is available, which is a most disturbing position since coronary angiography is now almost an established clinical investigation.

Coronary interarteriolar anastomoses

One further example of a basic problem of myocardial ischemia on which there is little agreement and little real knowledge is that of the coronary interarteriolar anastomoses, yet the presence or absence of these will be a matter of life or death to many of us. As is well known, coronary artery atherosclerosis is usually patchy in distribution, often limited mainly or even wholly to one arterial branch, with the other main arterial branches remaining relatively clean and healthy. When satisfactory interarteriolar anastomoses exist between the diseased branch and the other main branches, then there can be severe narrowing and even occlusion of the diseased artery with remarkably little damage to the related area of myocardium. This is emphasized by Beck,[6] who rightly has said: "Drops of blood added to or taken away from an area of muscle made ischemic by arterial occlusion make the difference between life and death." Similarly, Blumgart and associates[7] also point out that "anastomotic circulation to an extraordinary degree may obviate any serious consequences of complete coronary occlusion." Indeed, when adequate coronary interarteriolar anastomoses exist, all main branches on each side may be distally occluded without death necessarily resulting. It is essential, of course, that those anastomoses be large enough to carry a sufficiency of blood to the ischemic area; capillary anastomoses are not sufficient. There is general agreement that such anastomoses must be interarteriolar in size.[7,12]

Thus there is no difference of opinion as to the vital importance of coronary interarteriolar anastomoses. However, although the subject has been studied for some 300 years, there is no general agreement on the genesis of such anastomoses. Indeed, there are two seemingly contradictory theories, each of which has strong support.

In the first theory, the current one, it is claimed that in normal individuals the coronary arteries are true end-arteries with no anastomoses. This was the view put forward by Cohnheim[13] in 1881 and, except for some much-overlooked publications by the French workers around 1920,[14,15] this view was not seriously questioned for over 75 years. To a great extent the wide acceptance of the current theory is due to a series of important papers published by Schlesinger and various co-workers between 1938 and 1957.[7,12] The conclusions of these workers were that, with few exceptions, *firstly*, the normal heart possesses *no* interarteriolar anastomoses, i.e., healthy coronary arteries are true end-arteries and *secondly*, in the heart functionally important interarteriolar anastomoses develop only in response to ischemia, i.e., where and when needed. The practical implications of such conclusions are obvious, and are extremely important; according to this theory all men are born equal, at least in regard to a lack of coronary interarteriolar anastomoses. By the current theory, where ischemia is of slow and increasing degree, as in coronary atherosclerosis, the anastomoses would develop *pari passu* with the slowly increasing atherosclerotic myocardial ischemia; thus, if and when occlusion of a vessel finally resulted, the patient would have an adequate alternative circulation and damage would be *minimal*—the worse the coronary artery disease the

better the patient's chances of surviving an occlusion. In other words, the suggestion is that the disease immunizes its sufferers against its worst effects.

This theory fails, however, to explain several puzzling features of the disease. It does not explain why, with approximately equal degrees of coronary artery disease, one man will die from his first occlusion whereas another will survive several. It does not explain the well recognized observation that coronary heart disease seems to run in families. Nor, since anastomoses may take weeks to develop, does the current theory explain how it is that many individuals can survive a relatively sudden onset of ischemia as in occlusion of a previously fairly healthy artery.

It is suggested that these anomalies may be explained by the newer theory. In this newer theory it is claimed that the majority of individuals are born with a greater or lesser number of functionally efficient or at least potentially functionally efficient coronary interarteriolar anastomoses, the pattern and degree of which may be an inherited characteristic.[12] It is also claimed that this is true of animals other than man.[14] According to this view the effect of ischemia is limited merely to dilating pre-existing channels; it cannot cause the formation of new channels.

Where does the truth lie, and how is it that with so much money and time already spent there is still no agreement on this most basic facet of coronary heart disease? To a great extent the contradictory findings are due to the differences in techniques used by different workers. This was pointed out 40 years ago and is still true today.[12] Most of our understanding of the anatomy of the coronary arteries has been gained from x-ray studies of coronary arteries perfused with radiopaque materials. However, in almost all such studies the heart has been perfused on the assumption that it possesses only two arterial systems, namely, the right and left coronary arteries. But this view of the coronary circulation is much oversimplified, and in fact the coronary circulation behaves as though it has from three to five separate circulations, viz., *on the left* the left circumflex and left anterior descending branches are always present plus a third main primary division which is present in one of every four individuals, and *on the right* the main right coronary artery is always present, but with a conus branch which varies in size, and possesses a separate orifice in a large majority of individuals.

Now, when each of these branches is cannulated separately during perfusion experiments, a pattern of anastomoses emerges which would seem overwhelmingly to favor the newer theory, i.e., that such anastomoses are pre-existing and not in any way related to the presence or absence of ischemia. These anastomotic patterns offer a bewildering variation from individual to individual, ranging as they do from one extreme with no anastomoses whatever to the other extreme with complete anastomoses throughout. Another common finding is an intermediate type of pattern, termed by us "differential anastomosis," in which there are anastomoses only to one portion of the heart. The great significance of these "differential anastomoses" is that their distribution is independent of disease in the arteries, e.g., there may be full anastomoses to a healthy vessel but none to the ischemic myocardium supplied by another vessel with most severe atherosclerotic narrowing. Also, a differential anastomosis is often found in individuals with severe anemia in whom ischemia presumably would have been uniform throughout the heart.

The practical implications of the newer theory are most important. It postulates that all individuals fall into one of two groups, namely, *the minority group* in whom there are no intercoronary anastomoses, and in whom occlusion of a major vessel will be followed by severe cardiac damage and even death, and *the majority group* who have a greater or lesser degree of congenitally acquired intercoronary anastomoses, and in whom even occlusion of a major vessel need not necessarily prove serious.

If it were known in advance of the development of disease of the coronary arteries which individuals had an adequate collateral circulation, it would aid greatly in the treatment and in the prognosis of coronary heart disease, e.g., those in

iduals with no anastomoses might benefit greatly by the institution of anticoagulant or other therapy long before their first symptoms develop. On the other hand, those individuals who were known to have potentially efficient interarteriolar anastomoses would naturally carry a much better prognosis. In such individuals measures aimed at enlarging the anastomotic channels to their maximum size could be expected materially to reduce both the death rates and the morbidity rates should coronary artery disease and/or occlusion eventually supervene. In this connection it was noted earlier that ischemia causes a dilatation of collateral channels, and it seems likely that other conditions may be equally effective in so doing. For example, it is the impression of the authors that when present, the coronary collateral circulation in the Bantu of South Africa is generally better than that in the European.[1] This may be a reflection of the differing way of life, the Bantu taking considerably more exercise than does the European; i.e., exercise may be a very potent dilator of pre-existing coronary interarteriolar anastomoses.

Although the complete elimination of coronary artery disease and *ipso facto* coronary heart disease will only come with the elimination of atherosclerosis, it is possible that such a happy state of affairs may be long delayed. Thus, it is important to try in the meantime to find other measures which will at least reduce the present appalling mortality and morbidity of coronary heart disease. Clearly, a most promising approach would be further research into intercoronary anastomoses and the measures whereby congenitally acquired small channels may be dilated into vessels of lifesaving size. It could also be expected that research on this problem would at the same time lead to a much greater understanding of the basic anatomy, physiology, and pathology of the heart and that this, in turn, would allow us to build on a much firmer foundation than at present.

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Clinical communications

The evaluation of patients who develop recurrent cardiac symptoms after mitral valvuloplasty

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The majority of patients with cardiac disability due to rheumatic mitral stenosis are benefited symptomatically and hemodynamically by mitral valvuloplasty. The number of patients who receive initial benefit from surgery but who develop recurrent cardiac symptoms several years after the surgical intervention has been reported to vary between 5 and 20 per cent. The number of patients who lose their initial improvement after operation appears to become greater for each year of postoperative follow-up. In the first 1,000 cases of mitral stenosis reported by Ellis, Harken, and Black, 228 patients had a return of symptoms postoperatively after having had significant symptomatic improvement for at least 1 year. This report deals with 52 of these 228 patients who were readmitted to the Peter Bent Brigham Hospital because of a return of cardiac disability after initial improvement.

Although preoperative assessment of patients with mitral stenosis is at times difficult, in general it is relatively straightforward and does not require cardiac catheterization.[1-11] However, the postoperative assessment of patients who have a return of disability has turned out to be much more difficult. The nature and causes of this difficulty are evaluated in this paper.

Method

The material consisted of 52 patients who had been previously operated upon for mitral stenosis, and who, following a period of variable improvement, had a return of disabling cardiac symptoms. Patients were excluded from this study who had discernible heart disease other than that of the mitral valve. The problem presented postoperatively in these patients was the assessment of the relative degree of severity of stenosis and insufficiency.

All patients were evaluated by history, physical examination, standard 12-lead electrocardiograms, and cardiac fluoroscopy. The electrocardiographic diagnosis of left ventricular hypertrophy was based on the sum of the S wave in Lead V and the R wave in Leads V or V being greater than 35 mm. and S-T segments being depressed and T waves inverted in the left precordial leads. Right ventricular hypertrophy was diagnosed when the R wave exceeded the S wave in Lead V. Combined

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ventricular hypertrophy was considered to be present when criteria for left ventricular hypertrophy were noted in the presence of a mean electrical axis which was either vertical or rightward. On the basis of the findings, a *clinical diagnosis* was made by one observer (L.D.). Subsequently a *corrected diagnosis* was made utilizing the findings obtained by cardiac catheterization, indicator-dilution methods, and surgical intervention as described below. This corrected diagnosis was used to establish the accuracy of the clinical diagnosis.

Similar criteria for making a clinical diagnosis and a corrected diagnosis were used in 50 consecutive cases of mitral stenosis *preoperatively*. The accuracy of the clinical diagnosis in the 50 preoperative patients was compared with that in the 52 postoperative patients.

Cardiac catheterization was performed in all 52 postoperative patients. Twelve patients had right, 22 had left, and 18 had combined right and left heart catheterization. Right heart catheterization was performed by standard techniques,[15] and left heart catheterization by direct left atrial puncture as described by Björk and associates[16] or by the transseptal technique.[1] Cardiac outputs were determined by indicator-dilution methods utilizing radioactive I[131] or Cardiogreen,[4-20] and pressure recordings were made with Statham pressure transducers. Phasic and electrically integrated mean pressures were recorded in all cases. Calculations of the area of the mitral valve and pulmonary vascular resistances were made.[21,22]

Indicator-dilution curves were analyzed by the methods of Korner and Shillingford[23] and others[24,25] for the qualitative assessment of mitral insufficiency. Surgical estimates of the severity of mitral stenosis and insufficiency were made by Dr. Dwight E. Harken and Dr. Harrison Black in 39 of the 52 patients subjected to reoperation.

Results

In the 50 consecutive patients with mitral valvular disease who had *never* been operated upon, clinical assessment was correct as defined in 47, or 94 per cent. This is in agreement with previous reports from this clinic.[11]

In the 52 patients who had had a previous mitral valvuloplasty with improvement and then a return of symptoms, clinical assessment was correct as judged by the same criteria in 38 instances, or *only* 73 per cent. Twenty-two, or 42 per cent, of the patients postoperatively had pure mitral stenosis, either persistent or recurrent, 12, or 23 per cent, had a mixed lesion of stenosis and insufficiency, and 18, or 35 per cent, had predominant free mitral insufficiency. In an attempt to determine the source of diagnostic error, we undertook an analysis of the clinical and laboratory findings in these three groups of patients.

In mitral stenosis the left ventricle is uninvolved, whereas in mitral insufficiency the left ventricle dilates and hypertrophies. Therefore, in symptomatic patients with mitral valvular disease the status of the left ventricle, more than any other single feature, is ordinarily the predominant single factor that determines whether stenosis or insufficiency is responsible for the disability. In the analysis of the postoperative evaluation of these patients, clues which suggest left ventricular involvement will be emphasized. Tables I to VI document the salient findings.

Symptoms. The symptoms were not helpful in differentiating patients with mitral stenosis from those with mitral insufficiency (Table I). All of the 52 patients had symptoms of pulmonary congestion, and many had symptoms of systemic congestion.

Postoperative time interval. Patients with pure mitral stenosis returned, on the average, 3 years after operation, whereas those with mitral insufficiency returned after an average of 4½ years. The significance of this difference is not clear.

Physical examination. The interpretation of the physical examination was often misleading (Table II). A thrusting cardiac *apical impulse* suggestive of left ventricular hypertrophy or dilatation was present in 5 patients with pure mitral stenosis. Three of these patients were over 50 years of age but had no hypertension or other apparent cause of strain on the left ventricle. A normal or right ventricular type of cardiac impulse was present in 5 patients with a mixed lesion, and in 3 with predominant mitral insufficiency.

All patients had mitral diastolic murmurs of at least Grade 2 intensity (on the basis of 6). Apical pansystolic murmurs were present in two thirds of patients with pure mitral stenosis. Despite many examinations by several observers, apical pansystolic murmurs were absent in one case of predominent mitral insufficiency and in 2 cases of mixed stenosis and insufficiency.

The character of the first heart sound and the pulmonic component of the second heart sound were not helpful in differentiating stenosis from insufficiency.

Electrocardiographic findings. The electrocardiograms (Table III) were misleading in 16 of the 52 patients, suggesting left ventricular hypertrophy in one and combined hypertrophy in 2 patients with pure mitral stenosis, and showing right ventricular hypertrophy alone in 7 patients with mixed lesions and in 6 with predominant mitral insufficiency. Not infrequently the electrocardiogram was unchanged from that observed prior to mitral valvuloplasty even though mitral insufficiency had replaced mitral stenosis.

Radiographic findings. These were misleading in 17 of the 52 patients (Table IV). Five patients with pure mitral stenosis showed definite evidence of left ventricular enlargement and 12 patients with significant mitral insufficiency showed no left ventricular enlargement although all demonstrated right ventricular enlargement. The left atrium was enlarged in all patients, and although the enlargement was generally greater in those with insufficiency, a giant left atrium was seen in 2 patients with pure mitral stenosis. Prominence of the pulmonary artery segments was as great in insufficiency as in stenosis. Calcification of the mitral valve was of greater frequency in mitral insufficiency, suggesting a more distorted valve and one causing greater surgical difficulty at the time of the first operation.

Physiologic measurements. The data are summarized in Table V. The average cardiac output was markedly reduced in all groups. Patients with mitral stenosis had slightly higher pulmonary arterial pressures and pulmonary vascular resistances. However these parameters were greatly elevated in patients with mixed stenosis and insufficiency as well as in those with predominant insufficiency. The overlap was so great that they were not helpful in differentiating the lesion in individual patients.

Although *Korner Shillingford analyses* of indicator-dilution curves do not give quantitative estimates of mitral regurgitation they have been used with approximately 95 per cent accuracy for qualitative assessment of the general magnitude of the regurgitation.[17] Assessment using this method was in substantial agreement with the *surgical findings* (see Table VI) in 39 patients who underwent reoperation which was carried out in all of the patients with pure mitral stenosis and mixed stenosis and insufficiency. In addition surgery was carried out in 5 patients with predominant insufficiency. At the time of operation slight mitral insufficiency was found in 7 patients who had essentially pure mitral stenosis and moderate insufficiency in 7 patients who had been classified as having mixed stenosis and insufficiency. The results of valvuloplasty were considered by the surgeon to be poorer than usual in these patients who underwent reoperation and the surgical risk of the second operation was higher (Table VI).

Discussion

The recurrence of disability after a period of initial improvement following mitral valvuloplasty may be due to a number of factors: (1) mitral stenosis, either persistent or recurrent, (2) mitral insufficiency, (3) recurrent rheumatic fever, (4) presence or development of other valvular lesions, (5) presence or development of other types of heart disease, (6) other unrelated diseases, and (7) any combination of these factors.

Ellis and colleagues have reviewed the experience of this clinic and have reported that of the first 1 000 patients who underwent mitral valvuloplasty, 228 became worse after having been improved significantly for at least 1 year after operation. Inadequate correction of the mitral stenosis occurred in 38 patients who developed recurrent symptoms, and a "less than satisfactory" correction was attained in 66 other patients in this group. Restenosis of the mitral valve was considered to be rare in this series of patients. However Lowther and Turner[21] have considered restenosis to be the leading cause of recurrent dis-

Table I. Symptoms in patients with postoperative mitral valvular disease

Symptom	MS (22 total)	MS-MI (12 total)	MI (18 total)
Dyspnea	22	12	18
Fatigue	15	10	15
Orthopnea	20	12	16
Paroxysmal nocturnal dyspnea	17	10	16
Edema	15	7	12
Hemoptysis	7	2	3
Chest pain	5	2	5
Arterial embolism	2	1	1

MS, Mitral stenosis. MI, Mitral insufficiency.

Table II. Physical findings in patients with postoperative mitral valvular disease

Finding	MS (22 total)	MS-MI (12 total)	MI (18 total)
Cardiac impulse			
Right ventricular	14	3	3
Left ventricular	2	2	6
Combined	3	5	9
Normal	3	2	0
Murmurs			
Mitral diastolic	22	12	18
Mitral pansystolic	14	10	17
Others*			
Aortic systolic	2	1	1
Aortic diastolic	5	5	2
Tricuspid systolic	5	2	2
Pulmonic diastolic	2	0	0
Sounds			
Increased mitral first	16	8	11
Increased pulmonic second	20	10	17
Opening snap	18	10	12

*These associated valvular diseases were considered to be clinically and hemodynamically insignificant.

ability postoperatively. Fifty-six or 24 per cent of the 228 patients had mitral insufficiency which was either found or produced at the time of operation. Recurrent rheumatic activity developed in 38 patients or 17 per cent and associated aortic valvular disease was thought to contribute to the recurrence of cardiac disability in 28 or 12 per cent.

The present study deliberately excluded all but the first two causes of recurrent disability. It is concerned only with trying to differentiate mitral stenosis from surgically predominant mitral insufficiency when recurrent disability developed after mitral valvuloplasty. Although eventually such differentiation may be unimportant, currently it is important because surgery for relief of mitral stenosis is eminently satisfactory whereas that for relief of mitral insufficiency is still in the preliminary stages of development.

The *preoperative* assessment of patients with mitral stenosis or with free mitral insufficiency is usually straightforward. If cardiac disability exists, the differentiation of stenosis or insufficiency depends above all on the character of the apex impulse, the size of the left ventricle radiographically, and electrocardiographic evidence of

Table III. Electrocardiographic findings in patients with postoperative mitral valvular disease

Finding	MS (22 total)	MS-MI (12 total)	MI (18 total)
Rhythm			
Atrial fibrillation	15	7	15
Normal sinus rhythm	7	5	3
Hypertrophy			
Right ventricle	17	7	6
Left ventricle	1	3	6
Combined	2	2	6
None	2	0	0

Table IV. Fluoroscopic findings in patients with postoperative mitral valvular disease

Finding	MS (22 total)	MS-MI (12 total)	MI (18 total)
Cardiac enlargement	18	12	18
Enlarged right ventricle	19	12	9
Enlarged left ventricle	5	6	12
Enlarged pulmonary artery	20	11	16
Enlarged left atrium	22	12	18
Calcification of mitral valve	5	3	10

Table V Hemodynamics in patients with postoperative mitral valvular disease

Findings	MS (22 total)		MS-MI (12 total)		MI (18 total)	
Cardiac Index (L./min./M.)	2 2		1 8		2 0	
Estimated regurgitation						
Number of patients	0		12		18	
Qualitative estimat	<1+		2 3+		3+	
Pressures (mm. Hg)	S/D	(Mean)	S/D	(Mean)	S/D	(Mean)
Pulmonary artery	76/38	(50)	69/36	(49)	54/26	(36)
Left atrium		(24 4)		(24 1)		(23 1)
Pulmonary "capillary" wedge		(26 4)		(22 0)		(21 6)
Left ventricular diastolic mean		(5 2)		(5 0)		(4 6)
Mitral valve area (sq. cm.)	0 7		†		†	
Pulmonary vascular resistance (dynes sec cm.⁻⁵)	689		745		338	

*Qualitative estimates using methods of Korner and Shillingford.[39]
†No calculations were made of the mitral valve area since the total mitral diastolic flow was not known.
S/D (Mean) Systolic/diastolic and mean pressures.

Table VI Findings at second operation in 39 cases of recurrent mitral valvular disease

	MS	MS-MI	MI
Unoperated	0	0	13
Operated	22	12	5
Regurgitation at operation			
None	19	0	0
Mild	3	5	0
Moderate	0	7	0
Severe	0	0	5
Estimated surgical results			
Excellent	9	0	0
Good	7	4	0
Fair	4	5	1
Poor	0	3	2
Operative deaths	2	0	2

right or left ventricular involvement. A real problem arises, however with the mixed lesion wherein both stenosis and insufficiency coexist each being moderately severe Here the clinical picture is as mixed as is the underlying physiology for the simple reason that there are hemodynamically significant amount of both stenosis and insufficiency. Even at the time of operation the anatomic challenge is the correction of each lesion Thus preoperatively the assessment of the mixed lesion is the only one presenting a diagnostic challenge.

The *postoperative* assessment, however is much more difficult and is not limited to the mixed lesion The findings in our patients indicate that, in those who have a recurrence of symptoms after an initial period of improvement postoperatively mitral stenosis may masquerade as mitral insufficiency or free mitral insufficiency may masquerade as mitral stenosis. In the patients with pure mitral stenosis, there were 5 instances of a thrusting left ventricular type of apex impulse in 3 the electrocardiogram suggested left ventricular hypertrophy although in 2 right ventricular hypertrophy was present as well and 5 had enlargement of the left ventricle in addition to right ventricular enlargement. These confusing findings were confined to 5 specific patients, 3 of whom were more than 50 years of age

In the patients with significant or predominant mitral insufficiency the apical impulse gave no suggestion of a left ventricular thrust in 8 in 3 there was no apical systolic murmur in 13 the electrocardiogram showed right ventricular hypertrophy without any suggestion of left ventricular

involvement and by x ray examination the left ventricle appeared to be of normal size in 12 patients. These confusing findings were scattered randomly among the patients with mixed lesions and those with predominant insufficiency

It is not always clear why the postoperative disease fails to give a clear clinical picture. However several factors appear to play a causative role *First* stigmata of the preoperative disease process tend to persist postoperatively It will be recalled that satisfactory relief of mitral stenosis is frequently not accompanied by changes in murmur electrocardiogram or cardiac silhouette Even when mitral insufficiency is exchanged for mitral stenosis at the time of operation the clinical manifestations of mitral stenosis may be retained and those of mitral insufficiency may not emerge sufficiently to be recognizable *Second* a larger number of patients have a mixed lesion of mitral stenosis and insufficiency postoperatively than preoperatively but as mentioned above this was not the sole cause of difficulty in clinical assessment This group comprised 12 of the 52 patients in this series An erroneous clinical diagnosis was made in 6 patients in this group *Third* the postoperative patient is of course older than the preoperative patient. With the passage of time left ventricles become enlarged In the patients with mitral valvular disease in whom assessment of left ventricular size is so important, we have been impressed with the frequent *slight but definite* enlargement of the left ventricle in those who are over the age of 50 even when the rheumatic lesion is pure mitral stenosis. Three of the 5 patients with pure mitral stenosis and left ventricular enlargement, as evidenced by x ray study were over the age of 50

The error of postoperative assessment by clinical means alone was inordinately high (27 per cent) as compared with a similar group of preoperative patients in whom the error was 6 per cent The difficulty and unreliability of assessment in the postoperative patient indicated that the usual diagnostic criteria for differentiating mitral stenosis from insufficiency was unsatisfactory A number of patients who were considered to have predominant mitral insufficiency on clinical grounds were found instead to have pure mitral stenosis. Since the decision for surgical intervention depends on accurate diagnosis, it has become almost routine to employ cardiac catheterization plus one or another of the current methods for assessing mitral insufficiency in this group of patients. This has been considered to be necessary in order to recognize mitral insufficiency that mimics mitral stenosis and to ensure that surgical intervention not be denied those who have mitral stenosis which presents as mitral insufficiency

Summary and conclusions

Fifty two patients with mitral valvular disease in whom cardiac disability recurred 2 to 7 years after mitral valvuloplasty have been studied clinically and hemodynamically Recurrent or persistent mitral stenosis was present in 22 patients predominant mitral insufficiency in 18 and a mixed lesion of stenosis and insufficiency in 12. The inaccuracy of clinical assessment of these postoperative patients was 27 per cent, as compared to 6 per cent in 50 comparable patients who had never undergone a cardiac operation *Although* it is not entirely clear why postoperative assessment of mitral valvular disease is notably less accurate than preoperative assessment, three factors appear to cause the predominant difficulty First the physical findings, size and shape of the heart by x ray study and the electrocardiographic changes of mitral stenosis often persist postoperatively *Despite the substitution* of insufficiency for stenosis the preoperative manifestations of stenosis may persist It is possible that more mitral regurgitation is required to alter the clinical picture to that of mitral insufficiency under these circumstances. Second a larger number of postoperative patients return with the findings of mixed mitral stenosis and insufficiency and this is the classic group in whom under any circumstances, it is difficult to evaluate the predominant valvular lesion Third it has been our experience that patients over 50 years of age with pure mitral stenosis may present with clinical findings of biventricular enlargement which lead to the erroneous conclusion that mitral regurgitation is present

In the selection for reoperation of

Evaluation of new single, oblique chest lead for the rapid screening of electrocardiographic abnormalities in large populations

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Finding significant electrocardiographic abnormalities often makes it possible to recognize heart disease which is undetectable by other techniques, such as chest x-ray examination and physical examination of the patient. Simple, rapid, and reliable electrocardiographic screening techniques are needed for surveys of mass population because the multiple-lead electrocardiogram is generally too time consuming and expensive for large-scale screening. We have studied a single oblique electrocardiographic lead which makes it possible to detect a high percentage of significant electrocardiographic abnormalities in a large number of subjects with minimum effort and maximum convenience. Application of the electrodes and recording the single-lead electrocardiogram required less than 2 minutes for each subject.

Methods

The single oblique lead was obtained by recording the potential differences between an electrode positioned just below the clavicle to the right of the sternum and an electrode placed at the left posterior axillary line two to three fingerbreadths below the tip of the scapula. This lead might be presumed to be approximately collinear with the mean electrical axis of P and QRS and therefore would have impressed on it horizontal, vertical, and sagittal components of the electrocardiogram. Thus it should be capable of detecting abnormalities in any plane.† This lead was recorded by placing the right arm lead wire on the anterior chest electrode and the left arm lead wire on the back electrode with the lead selector on Lead I. Variations up to 2 inches in any direction in actual placement of the electrodes did not alter appreciably the configuration of the tracing. A copper electrode connected to ground through the right leg electrode was grasped by the subject. A halter with the electrodes attached allowed the electrodes to be slipped into position easily without the subject's being required to disrobe (Fig. 1). Good contact without

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†This lead was suggested by Dr. Robert H. Bayley, Professor of Medicine.

tients who develop recurrent cardiac disability after mitral valvuloplasty car diac catheterization has become prac tically routine in the reaching of a judicious decision with respect to the predominant valvular lesion The correct evaluation as it bore on the decision with regard to re-operation was made in more than 90 per cent of these difficult cases by careful evaluation of the hemodynamic data in conjunction with the clinical findings.

The uthors are indebted to Dr Dwight E. Harken and Dr Harrison Black for allowing them t study these patient nd to make use of their findings t operation.

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The incidence and significance of pulmonic regurgitation after pulmonary valvulotomy

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A precordial diastolic murmur which suggests the presence of pulmonic regurgitation is frequently audible in patients who have had a pulmonary valvulotomy for the relief of isolated pulmonary valvular stenosis. When such a murmur is not heard postoperatively, the clinical assumption has usually been that the valve is competent.[1] On the other hand, the appearance of most congenitally stenotic pulmonary valves indicates to the surgeon that stenosis usually cannot be corrected effectively without the creation of a greater or lesser degree of valvular incompetence. Within recent years, hemodynamic as well as clinical methods for determining the presence and magnitude of pulmonic regurgitant flow and for assessing its physiologic significance have been developed. These techniques were employed in the study of 23 patients who had undergone pulmonary valvulotomy and conclusions concerning the incidence and significance of postoperative pulmonic regurgitation are presented in the report which follows.

Patients and methods

The records of all patients at the National Heart Institute who have undergone pulmonary valvulotomy were reviewed. In 23 of these patients an assessment of the competency of the pulmonic valve was possible postoperatively and they were selected for detailed evaluation. The presence or absence of pulmonic regurgitation was determined by a comparison of preoperative and postoperative clinical examinations and/or the results of indicator dilution studies carried out at the time of postoperative cardiac catheterization.[2,3] The patients ranged in age from 2 to 50 years. Preoperatively, each demonstrated the typical physical, electrocardiographic, and radiologic findings of valvular pulmonic stenosis with intact ventricular septum and this diagnosis was established in every patient by catheterization of the right side of the heart and selective angiocardiography. The right ventricular systolic pressures ranged from 50 to 187 mm. Hg; the average was 102 mm. Hg. In 5 patients interatrial communications were also demonstrated at catheterization. No patient had a diastolic murmur. In 22 of the patients, pulmonary valvulotomy was performed under direct vision utilizing general hypothermia (11 patients) or cardiopulmonary bypass (11 patients). In every open operation each identifiable commissure of

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the valve was divided from the central orifice to the annulus, and in 6 patients a portion of one or more valve leaflets was resected as well In one patient, valvulotomy was accomplished by closed transventricular incision and dilatation In no instance was a resection of hypertrophic infundibular stenosis deemed necessary [13]

At intervals, ranging from 6 to 42 months after operation the patients were re-evaluated by clinical examinations and repeat catheterizations of the right side of the heart. All had experienced striking symptomatic improvement and relief of stenosis was confirmed in each patient by a satisfactory reduction in the systolic pressure gradient across the valve. In 12 patients, pulmonic regurgitation was evidenced by the appearance postoperatively of a diastolic murmur along the left sternal border In the other 11 patients the competency of the valve was tested at catheterization by the indicator-dilution method previously described [11] A modified double-lumen catheter was positioned with its distal opening in the main pulmonary artery and it proximal one in the mid portion of the right ventricle. Dye was injected into the pulmonary artery while blood was simultaneously withdrawn from the right ventricle through a cuvette densitometer

Results

A summary of the preoperative and postoperative clinical radiographic electrocardiographic, and hemodynamic findings in the 23 patients is presented in Table I In all 11 patients in whom the indicator-dilution study was performed a significant quantity of dye was immediately detected in the right ventricle after it had been injected into the pulmonary artery indicating the presence of incompetence of the valve A typical curve recorded in one of these patients is reproduced in Fig 1 No attempt was made to assess regurgitant flow quantitatively In every patient however the fraction of dye regurgitated was large and greatly exceeded the small quantity of reflux which is occasionally seen in normal patients, and which has been attributed to the presence of the catheter Pulmonic diastolic murmurs were also present in 6 of the patients in whom regurgitation was evident at catheterization The diastolic murmurs which were audible and recordable in 18 patients were characteristically low pitched rumbling mid-diastolic in time and usually followed the second heart sound by a short interval (Fig 2) In several patients the combination of systolic and diastolic components resulted in a to-and-fro murmur over the pulmonic area. Of particular interest was the fact that in 5 patients in whom significant pulmonic regurgitation was demonstrated by indicator-dilution testing no diastolic murmur was audible even though a portion of the pulmonic valve had been excised in one of them (Table I)

Changes in heart size as evaluated by a comparison of preoperative roentgenograms with those obtained a year or more after operation were not striking Seven patients showed an increase in the cardiothoracic ratio ranging from 1 5 to 9 per cent Decreases in heart size were observed in 8 patients, but in only 4 of them was the change greater than 2 5 per cent. In the other 8 patients there was no significant postoperative change in the cardiothoracic ratio

The postoperative electrocardiograms, also obtained a year or more after operation revealed marked regression of right ventricular prominence in 22 of the 23 patients. This was evidenced by a decrease in the height of the R wave in Lead V and a shift of the mean electrical axis in the frontal plane toward normal In 6 patients the electrocardiogram returned to normal The one patient (F.S) whose electrocardiogram did not change significantly had a residual left-to-right shunt through a patent foramen ovale

The right ventricular and pulmonary arterial pressures recorded before and after pulmonary valvulotomy are listed in Table I In 2 patients the catheter could not be passed into the pulmonary artery at the time of the preoperative study The pulmonary arterial diastolic pressure decreased in 13 patients from 1 to 6 mm Hg after operation was unchanged in 2 patients and increased from 1 to 4 mm Hg in 6 patients. In 21 patients the average end-diastolic gradient between the right ventricle and the pulmonary artery prior

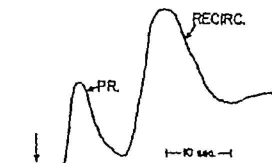


Fig 1 Indicator-dilution curve recorded with right ventricular sampling after injection into pulmonary artery The fraction of dye which appears immediately represents that regurgitated (*P R*) whereas the second larger deflection is dye normally recirculated The midpoint of injection is indicated by the arrow

to operation was 3 1 mm Hg The average gradient in these same patients after valvulotomy was only 1.3 mm Hg The end diastolic pressures in the right ventricle and the pulmonary artery were identical in 11 patients postoperatively (Fig 3) In another 11 patients the end-diastolic pressure in the pulmonary artery exceeded that in the right ventricle by less than 3 mm Hg These adjustments in diastolic pressure in the pulmonary artery were reflected in an increased pulse pressure in all but one patient

Discussion

A number of previous reports have indicated that pulmonic regurgitation may occur as the result of either an open[3,4] or closed[7] valvulotomy but it has been suggested that the incidence is higher after an open procedure since this approach allows wide incision of the commissures and removal of valvular tissue if necessary[1] As demonstrated by 16 of the patients in the present series, however a regurgitant valve may result even when no valvular tissue is removed It should be emphasized that the 23 patients described were selected from all those operated upon for pulmonic stenosis because the presence or absence of pulmonic regurgitation could be proved in them The indicator method for detecting pulmonic regurgitation requires the passage of a large double-lumen catheter a procedure which is impractical or impossible in many patients, particularly small children In every patient in whom this assessment was made after pulmonary valvulotomy the valve was proved to be incompetent The results of the present studies indicate therefore that any surgical procedure which adequately relieves pulmonic valvular stenosis must also render the valve incompetent

There is both present and past evidence to indicate that pulmonic regurgitation may exist in the absence of a characteristic diastolic murmur Hanson and co-workers[8] have demonstrated this phenomenon in a postoperative patient by means of selective pulmonary arteriography In 5 of our patients in whom regurgitation was confirmed by indicator-dilution methods no diastolic murmur was present, even though in one of them a portion of the pulmonic valve had been excised The explanation for the absence of a murmur in the presence of proved regurgitation is not clear although the small diastolic pressure gradient that exists between the right ventricle and the pulmonary artery in these patients is undoubtedly a factor It has been reported that with time a postvalvulotomy diastolic murmur may diminish in intensity or actually disappear[9] This phenomenon may be explained by the gradual approach of the diastolic pressure in the pulmonary artery to that in the right ventricle thereby abolishing regurgitant flow except during the earliest part of diastole The important fact remains that the absence of a diastolic murmur does not preclude the presence of pulmonic regurgitation

In the present study there is no evidence to indicate that the presence of pulmonic regurgitation in postvalvulotomy patients hinders their symptomatic improvement It is realized however that evaluation of postoperative symptoms is difficult and that, at best these are a poor index of hemodynamic change. The significant hemodynamic finding in these patients other than the decrease in or abolition of the systolic pressure gradient was a decrease in the end-diastolic gradient across the pulmonic valve and a corresponding increase in the pulmonary arterial pulse pressure. The association of these changes with pulmonic regurgitation has been substantiated both experimentally[11] and clinically[1,3] but only the presence of identical

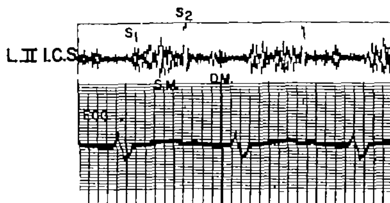


Fig. 2. Phonocardiogram of Patient J.S. after pulmonary valvulotomy. The record was made over the second left intercostal space. S_1 and S_2 indicate the first and second heart sounds, and *S.M.* and *D.M.* the systolic and diastolic murmurs.

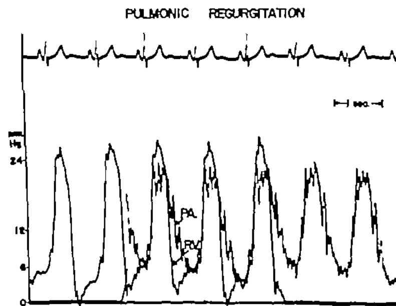


Fig. 3. Simultaneous records of pulmonary arterial (*PA*) and right ventricular (*RV*) pressures obtained postoperatively in Patient G.R. The presence of pulmonic regurgitation is indicated by the identical pressures at the end of diastole.

diastolic pressures offers diagnostic proof of the lesion.[11]

In the present series a satisfactory reduction in the pulmonic systolic pressure gradient was achieved in every patient, but the cardiac silhouette and cardiothoracic ratio remained relatively unchanged after valvulotomy. In many patients observations have been continued for periods of several years and have failed to demonstrate regression of the heart size to normal. In contrast to the lack of right ventricular regression shown by x-ray examination was the rather striking electrocardiographic evidence of decreased right ventricular hypertrophy. With one exception every patient showed a significant shift in the mean electrical axis of the heart and decreased right ventricular prominence indicated by regression of the

Table I Summary of clinical and hemodynamic findings before and after pulmonic valvulotomy

Patient	Preoperative pressures (mm Hg) PA S/D	PA Mean	RV S/D	Valve tissue excised	Grade of diastolic murmur (1-6)	Postoperative pressures (mm Hg) PA S/D	PA Mean	RV S/D	Pulmonary [illegible]	Cardiothoracic ratio Preop	Cardiothoracic ratio Postop	R wave Lead V1 (mm) Preop	R wave Lead V1 (mm) Postop
T.B.	16/8	11	55/5	–	0	21/6	12	28/5	+	47	49	40	14
V.D.	20/8	10	150/5	–	0	22/6	14	24/6	+	53	50	8	2†
C.F.	20/11	15	85/7	+	0	22/10	15	22/8	+	44	53	26	7
J.K.	15/9	10	145/5	–	0	15/5	13	30/5	+	45	45	4	2
J.G.	20/12	14	100/8	–	0	46/13	25	46/13	+	47	47	18	5†
E.H.	20/11	17	72/10	–	+	15/5	9	25/5		41	49	5	3†
K.G.	13/5	9	110/0	–	+	15/4	7	35/4	–	40	38	40	15
J.W.	23/12	16	155/12	–	+	17/8	10	56/6	–	42	43	17	4
F.S.	—	—	140/7	–	+	15/4	9	50/3	–	46	50	10	13
M.S.	25/10	15	90/2	+	+	25/8	12	50/6	+	41	38	25	10
R.H.	18/14	15	140/12	–	++	2[illegible]/12	19	40/12	–	38	36	70	4
M.C.	15/8	9	187/8	+	++	25/12	16	31/9	–	44	49	35	16
P.M.	12/5	9	50/3	–	++	23/6	11	30/6	–	48	48	12	7
D.K.	18/9	12	60/8	–	++	17/4	9	29/3	–	45	45	19	9
K.N.	15/5	12	70/2	–	++	18/6	9	50/6	–	45	50	11	5
R.J.	—	—	150/10	–	++	12/6	9	33/6	–	39	51	33	17
M.G.	14/7	11	65/2	+	++	30/10	15	31/2	+	41	45	11	7†
W.J.	14/6	7	78/2	+	++	17/6	10	45/6	+	43	48	5	
D.S.	12/8	11	100/4	–	++	21/7	13	28/6	+	41	41	6	0†
C.F.	12/7	9	54/3	–	+++	14/7	10	20/5	–	49	49	24	9
S.G.	10/4	6	50/2	+	+++	16/5	10	30/2	+	48	47	25	13
J.S.	15/8	11	81/5	+	+++	15/5	10	35/5	+	56	52	35	14
G.R.	25/12	17	130/8	–	+++	23/6	12	27/6	–	51	50	14	1†

*Patients with residual left-to-right shunts through patent foramen ovale.
†Electrocardiogram normal postoperatively.
PA: Pulmonary artery. RV: Right ventricle. Pressures are systolic, diastolic (S/D) and mean.

R wave in Lead V. In 6 patients the electrocardiogram returned to within normal limits although there was a slight average increase in the cardiothoracic ratios in these same individuals. This apparent discrepancy between the electrocardiographic and roentgenographic findings would suggest that after adequate valvulotomy muscular hypertrophy regresses, but that the regurgitation which inevitably occurs causes the chamber to dilate. This sequence has been substantiated in experimental studies of pulmonic regurgitation and presumably dilatation due to increased diastolic filling of the ventricle, predominates over the stimulus to hypertrophy occasioned by increased stroke work.[6]

A clinical opinion widely held is that pulmonic regurgitation is not a serious consequence of pulmonic valvulotomy.[3,4] Data obtained in patients with isolated pulmonic regurgitation without pulmonary hypertension also tend to substantiate this impression. Only one reported patient with isolated congenital valvular incompetence evidenced decompensation. All the others were either asymptomatic or only minimally so. Experimentally it has also been shown that severe degrees of pulmonic regurgitation do not preclude survival[11] and although the effective function of the right ventricle is compromised acutely[10] the burden imposed is one that an otherwise normal heart can accept. However it might be expected that the presence of another lesion which affects the right ventricle would alter this favorable outlook. Evidence that tends to corroborate this hypothesis is found in Patient F.S. in whom a residual left-to-right shunt, complicating pulmonic regurgitation was associated postoperatively with more severe x-ray and electrocardiographic evidences of right ventricular prominence. In 2 of the other 3 patients with residual left-to-right shunts the size of the heart increased and evidence of right ventricular prominence was still apparent electrocardiographically.

It may be concluded therefore, that pulmonic regurgitation of greater or lesser severity is an inevitable sequel of an adequate pulmonary valvulotomy. In the absence of complicating lesions, such as pulmonary hypertension or a circulatory shunt however it appears that the regurgitant flow is well tolerated and will not alter the favorable prognosis now presented to patients who must undergo operation for pulmonary stenosis.

Summary

Detailed clinical and hemodynamic studies were made in 23 patients after surgical correction of valvular pulmonic stenosis. In each, pulmonic regurgitation was shown to be present by the appearance of a diastolic murmur postoperatively and/or by the results of indicator-dilution studies made during postoperative cardiac catheterization. The latter method proved that the pulmonic valve was incompetent in every patient in whom it was applied including those in whom no diastolic murmur was audible. Satisfactory relief of stenosis was achieved in every patient but right ventricular prominence frequently persisted radiographically in spite of electrocardiographic evidence of regression of right ventricular hypertrophy. These findings suggest that the principal response to the incompetent valve is ventricular dilatation.

The results of the study indicate that pulmonic regurgitation is an invariable sequel to adequate pulmonary valvulotomy. In the absence of an associated lesion however the hemodynamic burden imposed by the regurgitant flow is apparently well tolerated.

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Ruptured aortic sinus aneurysms

Clinical and surgical aspects of seven cases

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Congenital aortic sinus aneurysm with cardioaortic fistula appears to be relatively rare, and it is our purpose to report 7 cases which were repaired with the aid of cardiopulmonary bypass.

The aneurysms arise most frequently from the right coronary sinus, less commonly from the noncoronary sinus, and rarely from the left sinus.

The fundamental lesion which predisposes to formation of an aneurysm is a lack of continuity between the aortic media and the annulus fibrosus of the aortic valve.[1]

The aneurysm is usually small and protrudes fingerlike into the right ventricle or atrium. Rupture at one or several places may occur at its presenting point with the formation of a cardioaortic fistula. In addition, the aneurysms may encroach upon intracardiac structures, interfering with the pulmonary or tricuspid valves or the conducting system. They may be associated with bulbar septal defects, anomalies of the aortic or pulmonary cusps, or subvalvular stenosis.

Although communication with the cardiac chamber may exist from the time of birth, the classic picture of ruptured aneurysm is very rare in childhood, and if in fact these aneurysms grow under the prolonged impact of aortic pulsatile pressure, rupture in later life rather than in early childhood might be expected. The classic picture is associated with the event of rupture, although the exact timing of the rupture is not always easily determined. Characteristically, there is sudden severe chest pain, which may occur with effort. The typical continuous murmur over the left side of the chest appears associated with a thrill in most cases. There is a wide pulse pressure and collapsing pulse and, after a latent period, heart failure with tricuspid incompetence. The classic history and physical signs usually enable the diagnosis to be made by clinical means.

The diagnosis may be substantiated by demonstrating the arteriovenous shunt into the right atrium or ventricle by means of catheterization of the right side of the heart and by delineating the pathway of the shunt by means of retrograde aortography.

The prognosis after rupture is variable; the patients may live from a few days to many years. The average age of patients

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Table I Clinical and operative findings in 7 cases of aortic sinus aneurysm

Case	Age sex	Blood pressure (mm Hg)	Cardiac enlargement	Thrill	Continuous murmur
I	41 F	190/0	LV+++ RV++	Systolic +++	2 LICS, Grade 6
II	31 F	135/50-0	LV++	Systolic ++	4-5 LICS, Grade 5
III	38 M	120/70	LV++	Absent	Xiphisternum, Grade 2
IV	52 M	150/0	LV++++ RV+++	Systolic and diastolic +++	2 to 5 LICS Grade 6
V	31 F	125/65	None	Absent	Xiphisternum Grade 3
VI	9 M	118/40	None	Systolic +	4 LICS, Grade 4
VII	39 F	120/70	None	Absent	Absent

Cardiac enlargement and thrills graded + to ++++ slight to very marked.
Murmurs Graded 1-6 in intensity
LVH Left ventricular hypertrophy RVH Right ventricular hypertrophy LAH Left atrial hypertrophy VPCs Ventricular pre-
LCS, Left coronary sinus RV Right ventricle, RA Right atrium, LA Left atrium.

with rupture who have been examined at autopsy has been reported to be 34.9 years. The main causes of death are heart failure and bacterial endocarditis.

Surgical repair of the aneurysm has been reported in recent years including successful repairs under hypothermia and by means of cardiopulmonary bypass.[4]

The clinical and surgical findings in the 7 cases are summarized in Table I

Case reports

Case I L.M 41 year-old woman, had cardiac history which dated back to the age of 7 years, when heart murmur was heard. The murmur was again noted during her first pregnancy when she was 28 years old. Dyspnea began at 31 years of age, at which time diagnosis of patent ductus arteriosu was made on the basis of continuou murmur At operation a patent ductus, 5 mm. in diameter was found and divided. After division of the ductus a loud systolic murmur and thrill persisted over the region of the pulmonary artery but the continuous murmur was no longer present.

Four months later she had febrile illness accompanied by signs of pericardial tamponade. A pure culture of *Streptococcus viridans* was grown from the pericardial fluid. The patient recovered under intensive penicillin therapy

When she was 32 years old catheterization of the right side of the heart demonstrated probable ventricular septal defect and pulmonary stenosis. At this time a continuous thrill and murmur maximal in the second and third left intercostal spaces, were noted.

She was admitted to hospital at the age of 41 in congestive heart failure The blood pressure was 190/0 mm. Hg and a loud continuous murmur accompanied by a coarse systolic thrill was audible over the whole precordium, with maximum intensity at the inner end of the second and third left intercostal spaces. The second heart sound was markedly accentuated and closely split

An electrocardiogram showed left atrial and left ventricular enlargement and digitalis effect. The x-ray film is shown in Fig 1,A A retrograde aortogram demonstrated a leak from the aorta into the conus of the right ventricle (Fig 2).

OPERATIVE NOTE. A bicuspid pulmonary valve with pronounced stenosis and an opening of only 5 mm. in diameter was found. The stenosis was relieved so that the valve opening was 2 cm. in diameter A ventricular septal defect 2 cm. in diameter was found just beneath the aortic valve One of the aortic cusps was partially prolapsed into this defect. One-half centimeter above the defect was an aneurysm of the right sinus of Valsalva with a hole 5 mm in diameter in its center The aneurysm was excised and the ventricular septal defect was closed, with securing of the prolapsed area of the aortic cusp. The defect of the sinus of Valsalva was then closed

After cessation of cardiopulmonary bypass there was only faint thrill in the pulmonary artery due to eddy formation at the bicuspid valve. The aortic pressure was now 120/70 mm. Hg, as compared with pressure of 280/50 mm Hg prior to bypass.

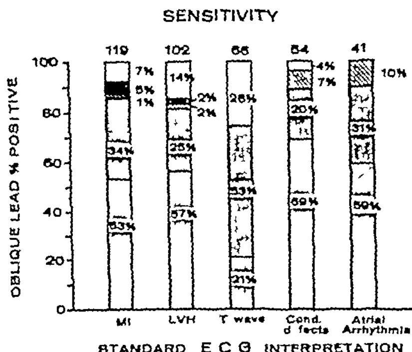


Fig. 3. Sensitivity of oblique lead as compared with the standard electrocardiogram. Comparisons are made on the basis of the presence of abnormalities, such as myocardial infarction (*MI*), left ventricular hypertrophy (*LVH*), primary T-wave changes (*T-wave*), atrioventricular and intraventricular conduction defects (*Cond. defects*), and atrial arrhythmias. The key is the same as that for the previous figure. The number of cases is shown for each category.

*Table I. Criteria used for the interpretation of the oblique single lead**

	Normal	*Suspiciously abnormal*	*Abnormal*
P deflection	Upright		Inverted
Amplitude	<3 mm.	3 mm.	>3 mm.
Duration	<0.12 sec	0.12 sec	>0.12 sec.
P-R interval	<0.20 sec.	0.20-0.21 sec	>0.21 sec
QRS form	qRs or rsR		
Duration	<0.11 sec.	0.11 sec	>0.11 sec
Q-deflection			
Duration	<0.03 sec.	0.03 sec.†	>0.03 sec
Amplitude	<3 mm.	3 mm	>3 mm
R deflection			
Amplitude	<25 mm.	25-30 mm	>30 mm
Peak time‡	<0.025 sec	0.025-0.03 sec.	>0.03 sec
R-ST junction	≦ .5 mm.	> .5 ≦1.0 mm.§	>1.0 mm
S-T segment	Isoelectric	Downward sloping	
T deflection			
Form	Upright	Flat	Inverted
Amplitude	1.5 mm	<1.0 mm. or >5.0 mm	

*Based on 105 normal tracings. Eighty-six of the oblique lead tracings fell within rigid limits.
†Present in 5 normal tracings.
‡Measured from baseline or initial notch on upstroke of R to peak of R when Q is absent in tracings.
§Present in 2 normal tracings.

Electro-cardiogram	Radiologic findings	Aneurysmal sinus	Fistula site	Associated lesions	Duration of illness (yrs.)
LAH, LVH, VPCs	Fig 1,A B Aortogram Fig 2	RCS	RV	Ventricular septal defect bicuspid pulmonary valve with stenosis	10
LVH	Fig. 3	NCS	RV	None	4
LVH	Fig 4	NCS	RA	None	5
LVH, RVH	LV+++ RV+++ LA+ PA++ Hilar pulsation. Aorta normal	RCS	RV	Fibrosis and thickening of all three aortic cusps	19
Normal	No enlargement. Pulmonary artery prominent. Aortogram Fig 5	NCS	RA	None	Unknown
LVH	Normal. Aortogram Fig 6	RCS	RV	Prolapse of RCS and aortic insufficiency	Since birth (?)
Inverted T in V_L. Flat T in V V	Aneurysmal bulge below pulmonary artery segment	LCS	LA	None	2

... contractions. LICS: Left intercostal space close to sternal edge. RCS: Right coronary sinus. NCS: Noncoronary sinus.

OPERATIVE DIAGNOSIS. Congenital aneurysm of the right coronary sinus with fistula into the right ventricle. Membranous ventricular septal defect with prolapsed aortic cusp. Bicuspid pulmonary valve with stenosis.

FOLLOW-UP The patient was well and symptom free 3½ years after operation. The heart had diminished in size, and only a Grade 3 systolic murmur was heard over the pulmonary area. Fig 1,B is an x-ray film taken 7 months postoperatively.

Case II N T 31 year-old woman, gave no history of heart disease or cardiac murmur until 4 years prior to admission to the hospital. At the age of 27 years she developed an upper respiratory infection and rapid heart action. Subsequently she experienced fatigue breathlessness and tightness of the chest with moderate exercise. Examination at that time was reported to have shown moderate cardiac enlargement blood pressure of 130/60-40 mm Hg and loud continuous murmur and thrill, maximum over the lower half of the left sternal edge. At that time the electrocardiogram was normal. A subsequent catheterization of the right side of the heart demonstrated the presence of left-to-right shunt in the right atrium (Ac).

Immediately prior to operation her main complaint was exertional fatigue. The blood pressure was 135/50-0 mm. Hg, with collapsing pulse. There was left ventricular enlargement and systolic thrill maximal at the fourth left intercostal space. The heart sounds were normal. A loud Grade 5 continuous murmur was heard maximally over the fourth and fifth left intercostal spaces.

An electrocardiogram revealed left ventricular hypertrophy. The x-ray film is shown in Fig. 3 A

OPERATIVE NOTE. The noncoronary aortic cusp appeared to be dilated. The right atrium and right ventricle were about twice normal size, and the pulmonary artery was one and one-half times normal.

When the right ventricle was opened, a pouch was seen to be arising from the base of the aorta, with an opening in the center. The pouch was excised and the remaining defect, 1 cm. in diameter was closed. After the operation there was no longer a thrill in the right ventricle. The blood pressure was now 120/70 mm. Hg as compared with pressure of 160/50 mm. Hg prior to cardiopulmonary bypass.

OPERATIVE DIAGNOSIS. Congenital aneurysm of the noncoronary aortic sinus with rupture into the right ventricle.

FOLLOW-UP An x-ray film taken 10 months after the operation is shown in Fig 3,B Three and one-half years after operation the patient has no abnormal physical signs in the heart and she is free of symptoms and leading a normal life.

Case III S.D 38-year-old man, was well, without a history of heart disease, until the age of 33 years, when he developed bacterial endocarditis. This was cured with penicillin. Examination during his stay in the hospital showed a blood pressure of 110/70 mm. Hg and a heart of normal size, with harsh parasternal systolic murmur and short diastolic murmur maximal at the third left intercostal space.

He remained well for the next 5 years and continued to work as a foreman for an oil company. Examination when he was 38 years old showed the blood pressure to be 120/70 mm. Hg. There was

A

B

Fig 1 Case I A Preoper ti -ray film B X-ray film taken 7 months after operation.

moderat cardiac enlargement, w th an pex beat of hea ing left entricular t pe A ystolic thrill could be felt over the third, fourth nd fifth left intercostal spaces, extending down over the xiphisternum. The heart sounds were normal A Grade 4 ystolic murmur maximal t the third and fourth left intercostal spaces, was heard. The murmur was ell heard over the xiphisternum. At the aortic area could be heard soft blowing diastolic murmur which as conducted down the left sternal edge. Over the xiphisternum the y tolic diastolic murmur wa continuous.

The electrocardiogram showed evidence of left entricular hypertrophy The x-ray film is shown i Fig 4,A

Catheterization of the right side of the heart demonstrated a left-to-right shunt t the atrial level, with moderate pulmonary hypertension (45/15 mm. Hg).

OPERATIVE NOTE. A thrill was palpable in the right trium and entricle near the border between the t o hambers. The right atrium and right entricle were greatly enlarged. When the right trium was opened and th aorta was cross-clamped, examination revealed a defect, 1 cm. in diameter the right trium t the base of the aorta. The aneurysm arose from the noncoronary cusp and had burrowed int the right trium.

OPERATIVE DIAGNOSIS. Congenital aortic sinus neurysm of the noncoronary cusp with fistula into *the right atrium.*

FOLLOW-UP A postoper tive x ray film is show Fig 4 B The heart is much smaller than it had been preoperati ely There are no bnormal physi al findings 3 ears after operation, nd the patient has continued to work since completion of his con alescence

Case IV P F a 52 year-old man, had no history of heart disease as child, but he recalled severe febrile illness at the age of 13 years. Dyspnea on exertion began hen he was 29 years old. At the age of 33 years he was told, hile in a hospital for pneumonia, that he had heart murmu H was ble to work as farm laborer until 10 years before operation, hen his breathlessness became more severe and began to be accompanied by distress in the chest nd und fatigue.

On examination he was breathless on mild exertion and the pulse was collapsing, with blood pressure of 160/0 mm. Hg The heart was greatly nlarged with hea ing left entricular apex beat the seventh intercostal space in the midaxillary line There was prominent parasternal right entricular lift ith igorous pulmonary closure tap in the second left intercostal space.

A marked thrill as felt in the second and third left intercostal spaces in systole, and in the fourth nd fifth intercostal spaces in diastole. The second heart sound was greatly accentuated A Grade 6 continuous murmur was heard from the second t the fifth left intercostal paces, close to the sternum but with wide radiation over the hest The systolic element of the murmur was loudest in the pper chest, the diastolic in the lower chest The electrocardiogram showed left and right entricular enlargement. The x-ray film is shown in Fig 5.

OPERATIVE NOTE. The right coronary sinus was aneurysmal and had ruptured through three openings into the outflow portion of the right ventricle The right atrium, right entricle, and left entricle were all markedly enlarged and dilated. The aorta was small the pulmonary artery was greatly dilated and tense

The redundant tissue around the fistulous openings was excised and the fistulas were closed, with obliteration of the neurysmal sac. After operation the blood pressur wa 120/75 mm. Hg and the heart rhythm was regular

On the second postoperati day trial fibril-

lation developed with a ventricular rate of approximately 150 per minute the blood pressure fell to about 90/60 mm. Hg. The ventricular rate was brought under control with intravenous ouabain, but the blood pressure did not rise. Ventricular fibrillation developed 6 hours later and resuscitation was unsuccessful.

OPERATIVE DIAGNOSIS. Aneurysm of the right coronary aortic sinus with fistula into the right ventricle.

POSTMORTEM EXAMINATION. The heart weighed 790 grams. There was moderate to marked generalized coronary atherosclerosis, with multiple focal occlusions of the right, left descending, and left circumflex coronary arteries. No old or recent thrombus or myocardial infarction could be identified. There was marked hypertrophy of the right and left ventricles. The right coronary sinus was dilated, and at the site of the aneurysm there was failure of continuity of the media of the aorta with the aortic valve ring. The right coronary cusp was fibrotic and calcified. The left and noncoronary cusps were fibrotic and thickened and the aortic ring was dilated.

MICROSCOPIC DESCRIPTION. The ventricular wall showed scattered foci of fibrosis, with larger areas of patchy dense fibrosis in the anterior septum. In section through the lower portion of the ascending aorta and extending to the wall of the aneurysm of the right aortic sinus the elastic and collagenous fibers of the aortic media were seen to stop almost abruptly at the upper margin of the sinus of Valsalva, and the sinus itself was lined only by thin layer of fibrous tissue approximately one fifth the width of the aortic wall.

Case 5. J.F., 31-year-old woman, enjoyed excellent health until 3 years prior to admission to hospital, during which period she had experienced easy fatigability and decreased physical endurance. A heart murmur had been noted at the time of routine examination when she was 22 years old. When she was 28 years old, the murmur was described as being continuous. At the age of 28 years she had had spontaneous abortion, and year later normal full-term pregnancy. She entered the hospital for diagnosis and treatment of heart condition.

The blood pressure was 125/65 mm. Hg. The heart was not enlarged. The only abnormal finding was high-pitched, blowing, typically continuous murmur which was heard maximally over the lower sternal region, with maximal intensity over the xiphisternum.

An electrocardiogram was normal. X-ray films showed no cardiac enlargement, but the pulmonary trunk was moderately dilated and the hilar arteries were prominent and showed moderately increased pulsation at fluoroscopy.

Catheterization of the right side of the heart revealed left-to-right shunt at the atrial level, with normal intracardiac pressures. Aortography was performed and outlined an aneurysm of the noncoronary sinus with fistulous track into the right atrium (Fig. 6).

AT OPERATION. A marked thrill was felt in the right atrium just proximal to the atrioventricular groove. The fistula arose from the noncoronary cusp and entered the right atrium approximately 5 mm. above the origin of the tricuspid valve. The aneurysm protruded into the atrium and was 7 mm. long and 7 mm. wide, with terminal opening 4 mm. in diameter. The aneurysm was excised and the defect closed.

OPERATIVE DIAGNOSIS. Aneurysm of the noncoronary aortic sinus with fistula into the right atrium.

FOLLOW-UP. The patient made an uneventful recovery and 18 months after operation she is in excellent health with no abnormal physical findings in the heart.

Case 11. J.P., 9-year-old boy complained only of heart murmur which was said to have been present since birth. At the age of 4 years he underwent heart surgery for suspected ductus arteriosus. The ductus was found to be obliterated and further operation was not attempted.

On examination the blood pressure was 118/40 mm. Hg, with collapsing pulses. The heart was not enlarged clinically. There was faint systolic thrill in the third and fourth left intercostal spaces close to the sternum. The heart sounds were normal. There was typically continuous murmur over the left chest, with maximal intensity at the inner end of the fourth left intercostal space. The electrocardiogram showed left ventricular hypertrophy. X-ray films showed the heart to be normal in size. The aortic arch was normal and there was slight prominence of the pulmonary artery trunk.

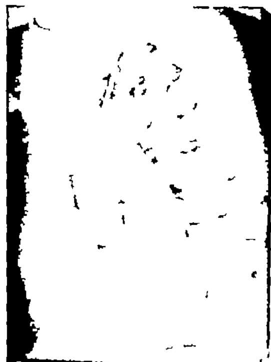


Fig. 2. Case 1. Retrograde aortogram. Leak of contrast medium from the right coronary sinus into the outflow tract of the right ventricle.

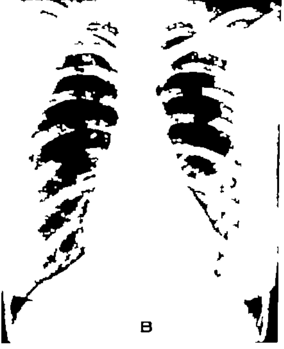



Fig. 3. Case II. *A*, Preoperative x-ray film. *B*, X-ray film taken 10 months after operation.

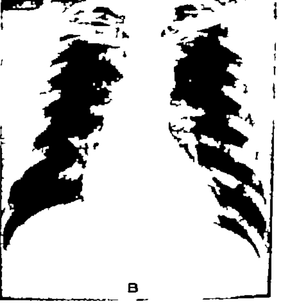



Fig. 4. Case III. *A*, Preoperative x-ray film. *B*, X-ray film taken 5 months after operation.

A retrograde aortogram showed an aortic sinus aneurysm from the right coronary sinus leaking into the right ventricle. There was considerable associated aortic insufficiency (Fig. 7).

Catheterization of the right side of the heart showed a left-to-right shunt into the right ventricle with normal intracardiac pressures.

OPERATIVE NOTE. A defect approximately 1 cm. in diameter was found posterior to the tricuspid valve. The tricuspid valve was detached at its most medial aspect, and the defect was seen to arise in the right coronary sinus. The cusp prolapsed toward the defect, which was repaired with interrupted sutures.

After repair a fine diastolic thrill was felt in the left atrium. Contrast medium was injected into the aorta, and an -ray film was taken. This revealed moderat aortic insufficiency Because of the patient's small size further repair was not ttempted.

OPERATIVE DIAGNOSIS. Congenital aortic sinus aneurysm of the right coronary cusp w th perforation into the right ventricle. Prolapse of the right coronary cusp with aortic insufficiency

FOLLOW-UP Six months after operation the patient is free of symptoms, but with clinical signs of moderate aortic insufficiency The heart size remains normal.

Case VII P h., a 39-year-old woman (case previously reported in *Circulation* 20 427 1959), had been well until 3 months before admission to the hospital, when she began to note gradually increasing weakness, dizziness, and exertional dyspnea. Her past illnesses included only measles, mumps, chicken pox, and whooping cough in childhood.

There were no abnormal physical signs in the cardiovascular system. Her blood pressure was 120/70 mm Hg.

An -ray film showed 6 by 6 cm. mass t the posterolateral aspect of the left cardiac border Comparison with films taken 2 years previously t another hospital showed a ery marked increase in the size of the mass during that time.

Catheterization of the right side of the heart and angiocardiography failed to determine hether the mass was intracardiac or extracardiac. The cardiac catheterization findings were normal.

Electrocardiograms showed T wave in ersion in Leads I and V and flattening in Leads V and V.

A thoracotomy was performed in anticipation of finding an extracardiac tumor The left trium was found to be markedly distended and tense from the presence of hard, nonpulsating mass which seemed to nderlie the entire anterior wall of the left atrium The mass pressed on and distorted the left circumflex coronary artery

Two months later second operation was per formed using cardiopulmonary bypass. An ncision was made into the left trial wall overlying the mass. A ca ity 7 cm. in diameter was entered and several large clots evacuated. A jet of bright red blood was found t be spurting from he base of this ca ity This jet originated from an opening 7 mm. in diameter the base of the aorta and was synchronous ith the arterial pump. When the jet was occluded, blood was seen to ooze into the cavity through several small pin-point openings which were found connect with the lumen of the left atrium. The intramural mass had nearly compromised the left rial ca ity and had partially oc cluded the mitral opening The left atrium was opened through second trial incision, superior and posterior to be first The mitral al was found to be normal as as the entire lining of the lef trial chamber A primary fistula hich opened t the base of the lef aortic sinus was closed and the secondary atrial openings were also closed. The sides of he dissected trial wall were then reapproximated After repair the left trium ppeared to be normal in size and configuration.

Two months after operation the patient had none of her preoperati symptoms, and the ECG had returned to normal. She is known to be well and free of symptoms 4 years after the operation.



Fig 5 Case IV Preoperati -ray film. At post mortem examination the heart weighed 790 grams.



Fig 6 Case V Catheter introduced into the femoral artery passed through the aortic sinus to the right trium fistula. I jection t fistula filling aortic sinus, right trium, entricle, and pulmonary artery



Fig. 7. Case VI. Retrograde aortogram showing aneurysm of right coronary sinus and regurgitation of contrast medium into the left ventricle. Later films demonstrated leak of contrast medium into the right ventricle.

Discussion

Aortic sinus aneurysms are rare lesions but these 7 patients were seen within a 2 year period having been referred to us as possible candidates for operation. Two of them (Cases I and VI) had had previous thoracotomies one for a small patent ductus arteriosus and the other for a suspected patent ductus which was not found at operation

The ages of the patients ranged from 9 to 52 years and there was no sex predominance

If Case VII is excepted a continuous murmur was the essential physical sign of the cardioaortic fistula in each patient. No other sign appeared to us to be characteristic of this lesion The murmur varied from faint to extremely loud and audible with a stethescope just removed from the chest wall In Case III the continuous murmur was soft and difficult to hear An intravenous injection of 5 mg of methoxamine increased the blood pressure from 110 70 to 140 95 mm. Hg and decreased the heart rate from 94 to 73 per minute. This simple measure greatly increased the loudness of the continuous murmur allowing confident interpretation of its character

In 3 patients the murmur was accompanied by a systolic and diastolic thrill and in 2 by a systolic thrill only

The murmurs had a superficial quality when compared with the familiar murmur of patent ductus arteriosus. More important in the distinction from patent ductus was the site of maximum intensity of the murmur

In the 4 patients with fistulas into the right ventricle the murmurs were located over the second and third fourth and fifth fourth and second to fifth intercostal spaces at the left sternal edge, respectively whereas the 2 patients with fistulas into the right atrium had a localization of the continuous murmur over the xiphisternum and the areas immediately laterally The continuous murmurs in these 2 patients did not extend higher in the chest. We think that the distinction between right ventricular and atrial perforations can be made, on occasion by the localization of the continuous murmur In no case was the murmur loudest at the second left intercostal space and above as is so common in patent ductus arteriosus.

The associated deformities—ventricular septal defect prolapsed aortic cusp and pulmonary stenosis in Case I sclerotic aortic valve in Case IV and prolapsed aortic cusp in Case VI—did not distinctly alter the physical signs the continuous murmur was the cardinal sign in each case.

Four of the patients had wide pulse pressures and collapsing pulses which suggested an aortic leak. During the period in which these patients were studied 2 other patients were seen with collapsing pulses and rough systolic and diastolic murmurs along the left sternal border accompanied by systolic thrills. The murmurs were not continuous and the patients proved to have ventricular septal defects associated with prolapsed aortic cusps. Two other patients had soft continuous murmurs located over the fifth left intercostal space midway between the sternum and the cardiac apex beat. The heart was normal in size in both patients. In one the electrocardiogram was normal and the x-ray films revealed a pulmonary arteriovenous fistula in the lingula of the left lung In the other patient the electrocardiogram showed marked left axis deviation

only. Cineangiocardiography demonstrated a left coronary arteriovenous fistula which emptied into the outflow portion of the right ventricle.

The electrocardiograms of these 7 patients showed no diagnostic features, usually showing left ventricular enlargement, but with a normal tracing in one adult.

Radiologic studies have shown changes which varied from a normal-sized heart with prominence of the pulmonary artery segment to enlargement of all chambers, including the left atrium and pulmonary plethora. Although there was an aortic leak the aorta was prominent in only 2 patients.

Retrograde aortography proved to be a safe and valuable method for demonstrating the course of the fistula after the left-to-right shunt had been detected by catheterization of the right side of the heart. In the 3 patients in whom aortography was performed the fistula and the chambers into which shunting occurred were outlined and in one patient the catheter was passed from the aorta through the fistula into the right atrium. The injections of contrast medium were made immediately above the aortic valve using pressure injection without aortic occlusion.

It seems peculiarly difficult to reconstruct accurately the episode of rupture in these patients but this may be due in part at least to the fact that all these patients survived the rupture by several years. Review of the case histories suggests that the rupture occurred at least 10, 4, 19, and 2 years prior to operation in Cases I, II, IV, and VII respectively. In Case V there was no clinical episode to suggest rupture and in Case VI the 9-year-old boy the presence of a murmur shortly after birth and the operation for suspected ductus when he was 4 years old lead us to suspect that the fistula was present at birth.

In Case III the patient was well until he developed staphylococcic endocarditis 3 years before operation. Previous examination had not revealed heart disease and it is likely that endocarditis began in an unruptured aneurysm and led to its perforation.

The surgical implications in instances of this lesion are evident from the published reports and the successful outcome in 6 of the 7 patients reported on here. Although our patients were operated on at a time apparently remote from the event of perforation and this event was not easy to identify retrospectively, a characteristic syndrome associated with rupture has been well documented and early operation with a high rate of cure should be possible in most cases.

Summary

1. Seven new cases of ruptured aortic sinus aneurysm are presented. All the patients were submitted to open-heart surgery with one operative death.

2. The characteristic continuous murmur of this lesion is discussed and the possibility of distinguishing right ventricular from right atrial perforations is noted. In the 2 patients with fistulas into the right atrium the murmur was localized to the xiphisternum and the area immediately laterally without radiation higher into the chest. The murmurs in the patients with right ventricular fistulas were heard over the second to fifth left intercostal spaces. None had a predominant radiation of the murmur above the second intercostal space as is common in patent ductus arteriosus.

3. The difficulty in determining the time of rupture of the aneurysm in these patients is stressed and in one case the fistula may have been congenital.

4. The condition is amenable to operation and most cases should be curable.

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Clinical and physiologic effects of antazoline, a new antiarrhythmic agent

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Following the reports of Graham and Craver, antazoline 2 (N-benzylanilinomethyl) 2 imidazoline) was introduced as an antihistamine.

Dutta and Burn and Dutta demonstrated that antihistamine compounds, including antazoline, possessed some pharmacologic properties in common with atropine, pethidine, procaine, and quinidine. In addition, it was suggested that antazoline reduced the depressant action of acetylcholine on the isolated rabbit atrium and decreased as well the maximal rate at which it would respond to electrical stimulation. Furthermore, it appeared to be about twice as potent as quinidine in its ability to prolong the refractory period of the atrium. Burn further postulated that antazoline, as well as other related antihistaminic compounds, could be used to restore a normal sinus rhythm in patients with atrial fibrillation. In 1952 McKechnie described the suppression of ventricular premature systoles by oral and intravenous antazoline and recommended that antihistaminic compounds be given a further and more extensive trial in cardiac arrhythmias. Angelakos and Hegnauer noted that several antihistaminic drugs, most particularly antazoline, were more effective than quinidine in suppressing spontaneous and surgically induced ventricular fibrillation in the hypothermic dog.

More recently, Brown demonstrated the effectiveness of antazoline in the prevention of ventricular fibrillation during cooling and rewarming experiments in a large series of dogs. Early observations suggested that antazoline was a highly effective agent in terminating ventricular tachycardia induced by sand injected into the anterior descending coronary artery. Further clinical studies confirmed the efficiency of this agent in both supraventricular and ventricular arrhythmias.

It is the purpose of this paper to report a large clinical experience as well as to demonstrate the hemodynamic and physiologic effects of antazoline.

Methods and materials

Five mongrel dogs which weighed from 12 to 25 kilograms were anesthetized with

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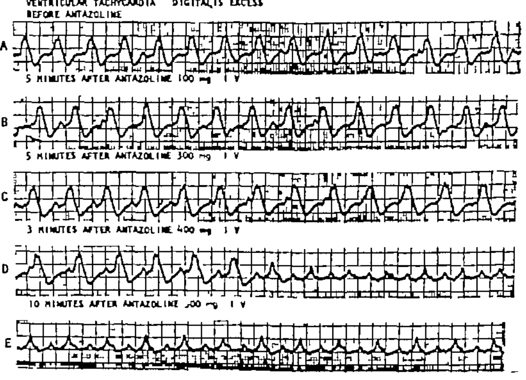


Fig 2 A E, Lead II trial flutter with complete A V dissociation due to ventricular tachycardia changes t 2 1 entricular response when ectopic entricular rhythm stops after antazoline.

constriction or from the myocardial depressive action of the agent is still unknown

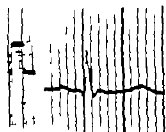
These hemodynamic responses are quite different from those of quinidine or procaine amide. With quinidine cardiac output and stroke volume are increased and peripheral vascular resistance is reduced. With procaine amide, there is very little change in cardiac hemodynamics. However an increase in the dosage level of either drug from 10 to 20 mg per kilogram caused a precipitous drop in blood pressure as well as in cardiac output.[11]

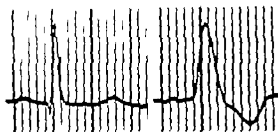
Although myocardial contractility was not specifically measured large intravenous doses (40 to 50 mg per kilogram of antazoline) in dogs progressively decreased contractility until the heart stopped in diastole. After an initial increase in the rate, there was usually a progressive slowing of the sinus activity followed by sinus arrest with an escape of an idioventricular pacemaker with bizarre and widened QRS complexes. Finally all electrical activity of the heart ceased Ventricular fibrillation was not observed with toxic dosage levels.

In only 2 cases was there a temporary increase in the QRS duration after intravenous antazoline. There was no increase in the Q-T duration in the clinical studies.

Several comments seem to be appropriate relative to the clinical study Antazoline proved to be equally effective in controlling atrial and ventricular ectopic beating regardless of etiology Furthermore, the drug proved to be quite safe in the presence of acute myocardial infarction and digitalis excess. In several instances the drug was utilized prophylactically to eliminate ectopic impulse formation prior to cardiac catheterization and cardiac surgery When a regular rapid mechanism is present it is not necessary to decide whether the rhythm is supraventricular or ventricular in origin before the drug is administered (Fig 4) The only exceptions would be rapid atrial flutter and fibrillation. In these arrhythmias the diagnosis is usually apparent.

There were no failures in the group of patients with atrial premature systole, and only 4 (6 per cent) failures in those with





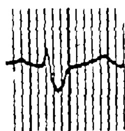


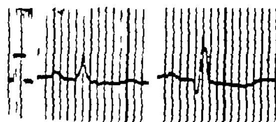
Fig 4 Cha acterist form obtained ith the oblique le d normal subject subjects ith left entricula h pertrophy (*LVH*) diagnosed by the tandard lec roc rdiogr m nd in subjects ith omplet left bundle branch block (*LBBB*) nd omplet right b ndle branch block (*RBBB*). I LVH incre sed ampl ude of R is noted Broaden ng of QRS inter l nd bsence of Q are seen with LBBB An in ial qR complex followed by broad S deflection are diagnost of RBBB The oblique le d w recorded t normal tandardization. I thi figure the rec rd ng paper peed 75 mm per second Time l nes re 0 01 sec

or suspiciously abnormal by the single lead (Fig 2) There were some abn rmal ties in the single lea l which were m ssed on the first reading which should have been recog nized These together with tracings show ing suspiciou features which were appre ciated later would hav brought the potential sensitivity r te to about 88 per cent

Suspiciously abnormal One hundred an l thirteen stan lard electrocardi gr m showed abnormalities, including possible infarction suggestive left ventricular hy pertrophy " or questionable T wave changes. The single-lead electrocardio gram was interpreted as abnormal or suspiciously abnormal in 35 per cent of these (Fig 2)

Correlation with specific abnormalities

Myocardial infarction (*Figs 3-6*) In anteroseptal infarction the Q deflection disappeared and there was often a pro longation in the upstroke time (onset of R to peak of R) of the R deflection in the single lead With other infarctions, a Q deflection of greater than 0 025 second was present It was greater than 4 mm in amplitude in posterior and lateral infarc tion but somewhat less in anterolateral and inferoseptal infarction Of all infarcts diagnosed from the standard electrocardio gram (119 definite and probable) 87 per



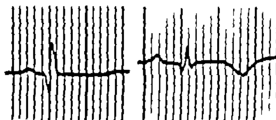


Fig 5 The oblique lead I myocardial infarction I a teroseptal infarction (*AS*) the initial Q de flection bsent and the pe k-time of R is pro longed. I a terolateral nd lateral inf rction (*ALL L*) the Q deflection is broad and deep. It is f g eater mplitude in posterolateral inf rct n (*PL*), nd f somewhat lesser amplitude in infero septal or diaphragmatic infarction (*IS*). In thi tracing (*IS*), increased ampl tude of the I w suggest left t ial hypert ophy Presen of prim ry T hange (late I ersion of T) de notes m ler t ly recent infarct (see lso Fig 6). St ndardizat on nd paper peed I Fig 4

ventricular premature systole. All but 7 patients of the latter group had a complete suppression of ectopic beats as counted in a 3-minute period. In 6 of 10 cases antazoline permanently terminated ventricular tachycardia.

Antazoline exhibited potent antiarrhythmic properties in the presence of digitalis excess. A sinus rhythm was re-established after antazoline in 2 cases of advanced A-V heart block. *One case of ventricular tachycardia* (Fig. 2), 6 instances of multifocal premature systoles, and 6 cases of nonparoxysmal nodal tachycardia were terminated by this agent. Paroxysmal atrial tachycardia with block proved to be an exception in that antazoline enhanced A-V transmission resulting in a 1:1 A-V conduction ratio and consequently a more rapid ventricular response. It is not known whether further use of this agent would have terminated the ectopic mechanism.

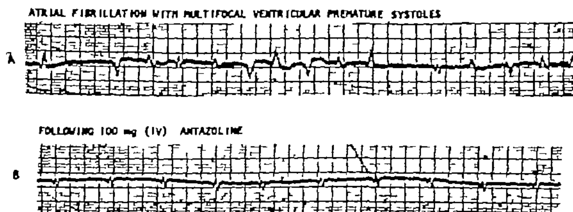


Fig. 3. *A*, Lead II. Atrial fibrillation is present with multifocal premature ventricular systoles due to digitalis excess. *B*, Four minutes after 100 mg. of antazoline intravenously the premature ventricular beats have disappeared. Atrial fibrillation continues with intermittent A-V dissociation due to acceleration of a nodal pacemaker.

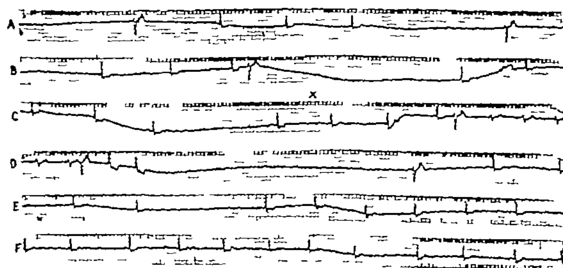


Fig. 4. *A,B*, Lead I, ectopic nodal tachycardia ... A-V block and ... nodal pacemaker with exit block of the Wenckebach type. *C-F*, Antazoline 300 mg. intravenously (X) first enhances ectopic pacemaker activity in the ventricle (*C, D*), later reduces exit block of nodal pacemaker (*F*).

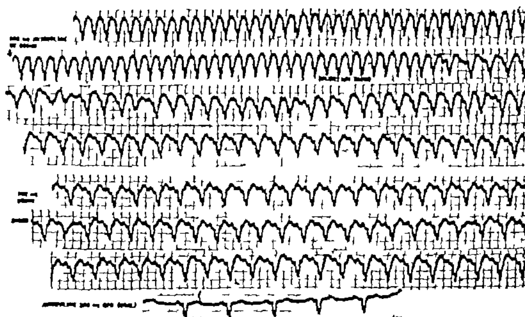


Fig. 5. Atrial tachycardia with 1:1 A-V and aberrant ventricular conduction. Antazoline causes, at first, irregular response (*end of second strip*), then slows and stops intermittently the atrial tachycardia, and finally stops it permanently so that a sinus tachycardia takes over (*… second section*). On the following day aberrant ventricular conduction has disappeared after further slowing of sinus.

since it was deemed advisable to withhold subsequent doses when the rapid ventricular rate occurred.

Enhancement of A-V conduction was observed in the presence of first-degree, second-degree, and advanced A-V heart block (Fig. 6). Furthermore, the ventricular response was invariably increased in the presence of atrial fibrillation due to enhanced A-V conduction. In one patient paroxysmal nodal tachycardia was terminated after antazoline (Fig. 7). In one instance of advanced A-V block secondary to acute myocardial infarction, antazoline increased the rate of the nodal pacemaker, thereby preventing Adams-Stokes attacks (Fig. 4). However, in the presence of advanced A-V heart block, the anti-acetylcholine effects of enhanced A-V nodal impulse formation and conduction may be overshadowed by the myocardial depressant effects of antazoline. This might result in suppression of all pacemaker activity.

Although antazoline has profound effects on cardiac hemodynamics and ectopic rhythms, the mechanisms for these effects remain largely unknown. If antazoline prolongs the refractory period of cardiac muscle, how can we explain its ineffectiveness in atrial fibrillation and flutter? A predominant anti-acetylcholine effect does not appear to be responsible for the antiarrhythmic properties, since the majority of the ectopic mechanisms studied are unresponsive to atropine. However, the enhanced A-V transmission and acceleration of nodal pacemakers may be a result of this effect. Perfusion studies on the isolated heart are now in progress to elucidate these mechanisms.[13]

After the successful termination of an ectopic tachycardia, subsequent administration of antazoline was not usually required. However, prophylactic oral antazoline was frequently given at the request of the clinician after successful conversion of an ectopic mechanism. Further study is required before the efficacy of this method is established. The therapeutic effectiveness of oral antazoline appears to be 4 to 6 hours. Hence, 100 to 200 mg. is required three or four times daily. The intravenous dosage can be repeated safely at intervals of 2 to 3 hours. However, in view of the profound myocardial depressant actions of this agent, it should be

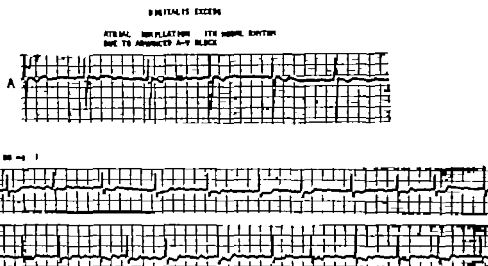


Fig. 6. *A*, Lead V, atrial fibrillation with advanced A-V block causing incomplete A-V dissociation (second beat is capture). *B-C*, Lead II. There is still considerable A-V block although to lesser degree than in *A*.

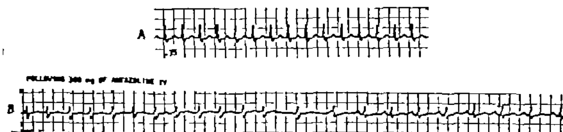


Fig. 7. *A*, Lead II, nodal tachycardia (172 per minute) with retrograde activation of atria. *B*, After 300 mg of antazoline intravenously the nodal rate slowed to 140 per minute with characteristic long and short cycle lengths of 0.40 and 0.46 second due to alteration of forward conduction and stable retrograde conduction. (Note alteration of "S waves" corresponding to regular retrograde P waves.) Beat 13 and 14 are nodal escape beats. Absence of broad S wave in beat 14 suggests interference with sinus impulse. Sinus rhythm is re-established at right side of the strip.

used with caution in patients with reduced cardiac output.

Summary

1. Intravenous antazoline caused a transient reduction in cardiac output and stroke volume. Blood pressure was maintained while peripheral vascular resistance increased.

2. Antazoline exhibited both direct myocardial depressant effects and anti-acetylcholine actions.

3. There was a complete suppression of atrial premature systoles in all 15 subjects studied. Atrial tachycardia was promptly terminated in 12 of 13 patients. However antazoline proved to be ineffective in the presence of atrial flutter and fibrillation.

4. All but 7 of 68 patients with frequent ventricular premature systoles had an adequate response to antazoline. Ventricular tachycardia was terminated by intravenous antazoline in 6 of 10 patients.

5. Antazoline proved to be effective in terminating ventricular tachycardia, multifocal ventricular premature systoles and nonparoxysmal nodal tachycardia due to digitalis excess. However 1:1 conduction resulted in 2 cases of paroxysmal atrial tachycardia with block engendered by digitalis excess.

Antazoline is as effective as well to

rated antiarrhythmic agent which may be used in the therapy of ectopic beating of atrial nodal or ventricular origin

Antazoline was supplied by Dr Edgar Jack, Ciba Pharmaceutical Products, Inc Summit N J

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Comparison of continuous long term heparin and oral anticoagulant therapy in patients with severe angina pectoris

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The use of heparin for long term anticoagulation is attended by certain disadvantages. These include (1) increased expense, (2) the necessity for parenteral administration, and (3) occasional allergic reactions. However, the following considerations suggest that, despite the disadvantages, heparin may be the drug of choice. (a) It has more widespread effects on the coagulation process.[4] (b) Once the desired dosage has been established, the effects of heparin are more predictable.[13,17] (c) This drug has an antilipemic or "clearing" action which is not possessed by the oral anticoagulants.[13,14]

The purpose of the present study is to attempt to answer the following question: Do the theoretical advantages of heparin balance its practical disadvantages for continuous long-range treatment of patients with severe angina pectoris?

Materials and methods

Selection of patients. One hundred and four patients were selected from the Private Medical Teaching Service of the University Hospital and Hillman Clinic of the University of Alabama Medical Center according to five basic criteria.

1. Previous severe myocardial infarction: one or more well-documented "poor risk" acute myocardial infarctions having occurred 4 weeks or longer prior to inclusion of the patient in this study. Although the infarction may have been recent or old, electrocardiographic evidence in the form of characteristic QRS abnormalities was an essential requirement at the time of the acute infarction.

2. Severe angina pectoris: pain due to coronary atherosclerosis occurring upon normal or less than normal activity, at an average frequency of one or more episodes per day. In the evaluation of anginal distress the system of using four grades of angina pectoris based on effort tolerance was followed,[47] and only Grade III or IV patients were included in the study.

3. Absence of certain conditions: exclusion of persistent hypertension (diastolic pressure consistently above 90 mm. Hg), valvular heart disease, poorly controlled diabetes, significant obesity (15 per cent above optimal weight), chest pain of other types (skeletal, gastrointestinal, respiratory, etc.) not easily differentiated from the patient's angina, and any noncardiovascular disability likely to cause death or morbidity within 3 years.

4. No contraindication to anticoagulant

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Table I Comparison of anticoagulant groups

	Type of anticoagulant	
	Heparin	Oral
Number of patients	53	51
Age (yr.)		
Range	43-69	41-68
Average	57	58
Sex		
Male	48	47
Female	5	4
Duration of coronary artery disease		
Range	2 mo. 12 yr	2 mo. 14 yr
Average	3-3½ yr	3-3½ yr
Previous infarctions		
Total number	73	75
Average per patient	1.4	1.4
Interval since last infarction		
Range	1 mo. 7 yr	1 mo.-6 yr
Average	1-2 yr	1 2 yr
Angina pectoris		
Acute preinfarctional	25	24
Chronic postinfarctional	28	27
Duration of recent exacerbation of angina pectoris		
Range	1 wk.-6 mo.	1 wk. 5 mo.
Average	4-5 wk.	4-5 wk.
Cardiomegaly (chest film)	27	23
Digitalis maintenance	22	18
Diabetes mellitus	8	6
Intermittent claudication	14	10
Previous cerebral vascular accidents	4	6
Recurrent transient cerebral ischemia	7	9

therapy absence of conditions in which such therapy might increase or precipitate bleeding The only exception was a known peptic ulcer that may or may not have been previously complicated by bleeding

5 Patient cooperation ability and willingness to follow instructions accurately to make competent observations and to return at regular intervals

The 104 patients maintained on continued anticoagulant therapy were collected over an 18-month period Approximately half or 53 of these patients were given concentrated aqueous heparin whereas the other 51 patients received either bishydroxycoumarin or warfarin sodium† They were then followed for 24 months unless treatment was terminated prematurely by death or discontinuation of the anticoagulant. The only cause for discontinuation resulted from complications secondary to the therapy Thus, two groups of similar size with equally severe coronary disease, manifested by Grades III to IV angina pectoris and one or more previous "poor risk" myocardial infarctions, were treated continuously with anticoagulants—53 with heparin and 51 with oral anticoagulant—for periods of 1 week to 24 months with an average duration of 22 and 21 months per patient respectively

Allocations of patients

Because of the conditions of availability and supply of heparin it was not possible to place the patients on the anticoagulants by alternating patient distribution. Initially 30 carefully selected patients were started on heparin followed by 30 critically matched patients being started on bishydroxycoumarin or warfarin sodium

*Supplied by Dr E. W Young, Medical Director Upjohn Company

†Supplied as Coumadin by the Endo Company

The allocation procedure was repeated placing 23 selected patients on heparin and then 21 matched patients on warfarin sodium. In essence, this resulted in two groups of patients being matched with one another in all aspects, except that one group received continuous heparin anticoagulation and the other received continuous oral anticoagulation (Table I).

Angina pectoris in these patients was classified into two groups because of probable prognostic differences (Table I):

1. Acute preinfarctional angina: the sudden onset of progressive anginal pain or the sudden adverse alteration in the pattern of stable angina pectoris. Angina which previously occurred only on effort now occurred at rest, especially in the recumbent position, and more commonly awakened the patient from sleep. The adverse alteration in stable angina pectoris can be precipitated by various extracoronary factors, such as severe emotional distress, unusual exertion, cold environment, hypoglycemia, an unusually large meal, excessive ingestion of salt, anemia, hemorrhage, ectopic tachycardia, hyperthyroidism, etc. Since these extracoronary factors do not reflect the true progression of the underlying disease, they were searched for and excluded. Acute angina was present 1 week or longer prior to inclusion of the patient in the study.

2. Chronic postinfarctional angina: the occurrence of nonprogressive stable angina pectoris within 8 weeks after onset of acute myocardial infarction, and present at least 4 weeks prior to the start of anticoagulant therapy.

Thus, the method of allocation also resulted in there being in each anginal group two matched series of patients, matched except for the different types of anticoagulant therapy which they received.

Anticoagulant medications

The group of 53 patients was given subcutaneous injections of concentrated aqueous heparin sodium, varying from 100 to 200 mg. every 12 hours or from 300 to 400 mg. every 24 hours. Most of the patients received 125 mg. or 150 mg. every 1 hours. This schedule was preferred since continuous therapeutic anticoagulation was more easily attained and the incidence of bleeding was less. A continuous therapeutic anticoagulation level was accomplished by maintaining the 3-tube Lee White clotting time just prior to the next dose of heparin at two to two and one-half times the patient's control time.[36,37] Clotting times were performed regularly during the first 3 to 4 days of therapy, primarily to check the adequacy of the dose. Once the clotting time was stable at the desired level, these tests were done only at monthly intervals.

The patient, or a member of his family, was taught to administer the injections of heparin slowly into the deep subcutaneous tissues of the anterolateral thigh, the lower abdominal wall, or the area just below the posterior iliac crest.

Warfarin sodium and bishydroxycoumarin were given to the first 1 patients started on oral anticoagulants and were continued for about 4 months, then a change to warfarin sodium was made. Initial anticoagulation was carried out in the hospital with daily prothrombin checks after a control determination. The prothrombin levels were estimated by the Quick one-stage method.[43,44] After a satisfactory level had been obtained, the test was carried out at intervals of 2 to 3 weeks. The optimal therapeutic range was arbitrarily considered to be 25 to 30 seconds, i.e., two to two and one-half times the control prothrombin time. This corresponds to a prothrombin activity of 15 to 25 per cent. In approximately 0 per cent of the patients on oral anticoagulants the prothrombin level was maintained in the therapeutic range almost constantly. In the other 30 per cent, good control was maintained 75 per cent of the time.

Clinical supervision of patients

All patients returned regularly at monthly intervals for clinical assessment until death, discontinuation, or 24 months of continuous observation were completed. Also, at the time of these visits blood was drawn in a fasting state for the determination of total serum cholesterol[45,46] in all patients and for the determination of the coagulation and prothrombin times in those patients receiving heparin and those receiving oral anticoagulants, respectively. An additional separate visit to the laboratory for the determination of the plasma

Table II Deaths recurrent myocardial infarctions and discontinuations

	Type of anticoagulant					
	Heparin	Oral	Heparin		Oral	
			Acute angina	Chronic angina	Acute angina	Chronic angina
Number of patients	53	51	25	28	24	27
Total patient months	1 193	1 106	568	625	511	595
Average patient months	22	21	23	22	21	22
Deaths						
Number	3	8	2	1	5	3
Per cent	5 6	15 7	8	3 6	21	11
Rate per 100 months	0 25	0 7	0 35	0 16	1 0	0 5
Recurrent myocardial infarction						
Number	6	14	4	2	9	5
Per cent	11	27 5	16	7 1	38	18 5
Rate per 100 months	0 5	1 3	0 7	0 32	1 8	0 84
Discontinuation						
Number	5	3	2	3	1	2
Per cent	9 5	6	8	11	4	7 4
Rate per 100 months	0 4	0 26	0 35	0 48	0 2	0 34

prothrombin time was necessary for the patients on oral anticoagulants

Both the group of patients on heparin and the group on oral anticoagulants received the same cardiovascular supervision and management as well as the same general medical care. The dietary regimen was similar for all patients. Total calories were in the amount necessary to maintain the patient's weight at approximately the level present when he was initially included in the study. There was no significant change in the weight of any patient during the period of observation. The fat content of the diet supplied about 35 per cent of the total calories. Unsaturated fats made up approximately 50 per cent of the fat calories. No formula diets or specially devised foods were used. Dietary restriction of salt was employed when indicated. Permissible activity or exercise was determined by the clinical status and symptoms of the individual patient. Regular exercise below the threshold of anginal pain and other symptoms was encouraged. Medications, such as sublingual nitroglycerin tablets nitroglycerin ointment (Nitrol) digitalis, diuretics sedatives etc. were given to all patients when indicated

Patients were advised and encouraged to stop smoking. No inequality existed in the distribution of smokers among the groups.

With the initiation of continuous long term anticoagulation therapy chest x ray film electrocardiogram (ECG) ultralow frequency ballistocardiogram (BCG)[10,14] and electrocardiographic exercise test[15] were obtained in all patients. These studies were repeated under the same conditions at intervals during the observation period

At the monthly clinical examinations, information was collected in regard to the characteristics of the anginal syndrome amount of physical activity grade of angina hemorrhagic episodes other complications and side effects of the anticoagulant drugs recurrent myocardial infarction congestive heart failure, grade of effort dyspnea thromboembolic phenomena intermittent claudication of lower extremities episodes of cerebral ischemia sense of well being diet medications and other new developments.

All patients were supplied with the proper antidote (vitamin K_1 oxide or protamine sulfate) for their particular anticoagulant drug and advised in writing

as to its use. Also given were anticoagulant identification cards which bore the name of the drug antidotes, blood type physician's name etc.

Concerted and determined efforts were made to follow with equal care all patients in this study. With the exception of an additional laboratory visit (prothrombin time) every month by the patients on oral anticoagulant the physician visits labora tory visits and laboratory procedure in the two groups were equal.

Discontinuation of anticoagulants was caused by major hemorrhagic episodes painful reactions at the site of injection of heparin and allergic manifestations secondary to the heparin. There were no other causes for the termination of anticoagulation therapy.

Assessment of results

The objective of this study was to compare the effectiveness of continuous long term heparin and oral anticoagulation in patients with marked coronary artery disease and severe angina pectoris. Since the two types of angina pectoris present in each anticoagulant group differed in prognosis it was necessary to separate them into therapeutic subgroups for the purpose of comparison. In this manner direct comparison could be made between the heparin and oral groups of each type of angina pectoris.

The main criteria of the result of treatment were objective—death and recurrent myocardial infarction. The graded assessment of angina and to a lesser degree other features of circulatory disorder were used as ancillary criteria. Also, any significant complications due to the two types of anticoagulation therapy were taken into account. Since the practical success or failure of the two anticoagulant regimens depended on the above mentioned criteria, the analysis of the clinical data concerned the comparison of these aspects between the heparin and oral groups.

Table III. Causes of discontinuation

	Type of anticoagulant	
	Heparin	*Oral*
Number of patients	53	51
Number of discontinuations	5	3
Causes of discontinuations		
Major hemorrhage	2	3
Allergic reaction	2	0
Injection-site reactions	1	0

Deaths, recurrent myocardial infarctions, and discontinuations

The number of deaths recurrent myocardial infarctions and discontinuations in each anticoagulant group and its subgroups are given in Table II. These data are expressed as per cent of patients and rate per 100 patient months of observation. Both recurrent infarctions and deaths were fewer in the groups which received heparin. Approximately half of the recurrent infarctions and deaths in patients with acute angina occurred within 3 months after the start of therapy. In the groups with chronic angina these events were more evenly distributed over the entire observation period. Death in 4 of the 7 patients with acute angina followed recurrent infarctions whereas death in the other 3 was sudden. In the patients with chronic angina sudden death occurred once and recurrent infarction preceded the other 3 deaths. Postmortem examinations were performed in 7 of the 11 patients who died and the clinicopathologic correlation was correct in all instances. Discontinuations were more frequent in patients receiving heparin. The fate of patients who discontinued therapy was similar in regard to deaths and recurrent infarction for comparative groups. Causes of discontinuations are listed in Table III.

Anginal pain

Anginal distress was evaluated at monthly intervals using four grades of angina pectoris based on effort tolerance. According to this gradation system the patients were classified into the following five categories: (1) marked improvement—increase in effort tolerance of two grades or more (2) much improvement—increase in effort tolerance of one grade (3) some improvement—increase in effort tolerance of less than one grade (4) unchanged—no change in effort tolerance

Table IV. The effect of anticoagulants on anginal pain in anginal groups

	Acute preinfarctional angina		Chronic postinfarctional angina	
	Heparin (25 patients)	Oral anticoagulant (24 patients)	Heparin (28 patients)	Oral anticoagulant (27 patients)
Angina pectoris				
Marked improvement	10	3	18	4
Much improvement	5	5	6	7
Some improvement	3	2	1	4
Unchanged	3	5	1	7
Deterioration	4	9	2	5

(5) deterioration—any decrease in effort tolerance or recurrent infarction.

The results of these monthly evaluations were summarized at the end of the study and are presented in Tables IV and V along with the average times when initial and maximal improvement occurred in these patients (Table V). Significant improvement occurred in all groups, but was greater in the patients on heparin. Not only was there a greater number of improved patients receiving heparin but their degree of improvement was also greater. In the patients with acute anginal pain who were receiving heparin 7 per cent improved in comparison with 42 per cent improvement in the group of patients with acute angina who were on oral anticoagulants. The difference was even greater in the patients with chronic angina: almost 90 per cent on heparin improved as compared to 55 per cent improvement in the oral group. This demonstrates an 81 per cent improvement in patients receiving heparin as compared to an almost 50 per cent improvement in those on oral anticoagulants. Definite and persistent improvement in these patients had to be established before the data were included. Decreased consumption of sublingual nitroglycerin tablets quantitatively paralleled the amount of improvement.

Table V. The effect of anticoagulants on angina pectoris

	Type of anticoagulant	
	Heparin (53 patients)	Oral (51 patients)
Angina pectoris		
Marked improvement	28	7
Much improvement	11	12
Some improvement	4	6
Unchanged	4	12
Deterioration	6	14
Time of initial improvement		
Range	1-8 wk.	2-12 wk.
Average	3-4 wk.	6 wk.
Time of maximal improvement		
Range	1-10 mo.	3-18 mo.
Average	3-4 mo.	7 mo.

Table V also demonstrates that the onset of definite and persistent improvement did not occur immediately but, in all groups, usually required a few weeks to become established. Transitory improvement was not considered. Heparin was somewhat more rapid in initiating the favorable response. Maximal relief of anginal distress required a few months of therapy in all patients. This relief was usually obtained in a shorter period with heparin.

Intermittent claudication and cerebral ischemia

Other clinical features of circulatory disorders such as intermittent claudication and transient cerebral ischemia were apparently benefited by the anticoagulants. Table VI depicts these effects in the two anticoagulant groups. Because of less exacting criteria for improvement and the

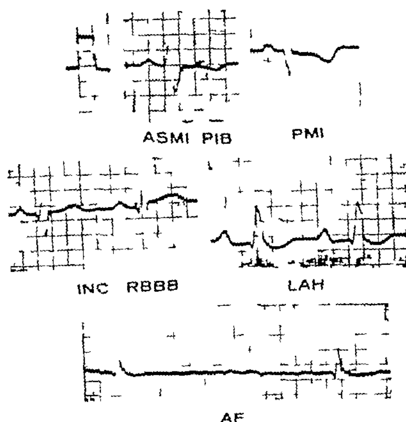


Fig. 4 The oblique lead in anteroseptal myocardial infarction with peri-infarction block (*ASMI PIB*), posterior myocardial infarction (*PMI*) incomplete right bundle branch block (*INC RBBB*), left atrial hypertrophy (*LAH*), and atrial fibrillation (*AF*). Activation of muscle units surrounding the dead zone in the anteroseptal region late in the QRS interval accounts for the S deflection in the oblique lead when anteroseptal infarction is complicated by peri-infarction block. A QRS interval of less than 0.10 sec. in the presence of right bundle branch block suggests that it is incomplete. The Q deflection in tracing *LAH* suggested anterolateral infarction confirmed by the standard electrocardiogram. Primary T-wave changes compatible with digitalis effect are seen in tracings *LAH* and *AF*. Normal standardization, paper speed 50 mm. per second. Time lines at intervals of 0.02 sec.

cent were detected in the single lead. Ninety three per cent might have been detected or suspected from the screening lead when abnormalities not recognized or appreciated on the initial interpretation are included.

Left ventricular hypertrophy. The amplitude of R in the single lead correlated well with changes in voltage seen in the standard tracing with left ventricular hypertrophy (Figs. 3 and 4). A downstroke of R of 0.05 second or more from its beginning was used as supplementary evidence of left ventricular hypertrophy. The ST T wave inversions commonly seen with left ventricular hypertrophy were generally present in the single lead. Eighty two per cent of the standard tracings with evidence of left ventricular hypertrophy were interpreted as abnormal or suspiciously abnormal by the single lead. In addition 48 per cent of the standard tracings showing suggestive left ventricular hypertrophy were read as abnormal or suspiciously abnormal in the single lead even though QRS abnormalities characteristic of left ventricular hypertrophy were not present. Nearly all of these tracings read as abnormal or suspiciously abnormal by the single lead were associated with T wave changes or other

smaller number of patients, the apparent superiority of heparin may not be so sig nificant as that found in the anginal syndrome. In view of the great variability in the natural history of untreated pa tients with episodic cerebral ischemia no conclusions are drawn concerning the dis- order

Cardiomegaly and congestive failure

Heart size was determined by measuring the transverse cardiac diameter on the standard posteroanterior chest films taken initially and at 6-month intervals. Com parison of the measured transverse diam- eters of the heart with the prediction table of normal transverse diameters for given heights and weights was taken as a rela t vely accurate indication of cardiac en largement. The number of patients with cardiomegaly at the start of the study was given in Table I There were only a few patients who showed an increase in their transverse cardiac diameter during the study and they were not predominant in any one therapeutic group

The typical symptoms and signs of a definit clinical response to digitalization indicated the presence or occurrence of congestive heart failure. These phenomena took place in only a few patients during the study and were equally distributed

Table VI Th effect of ant coagulant on intermittent claudicat on and cerebral s chemia

	Type of antic gulant	
	H pari (53 patients)	*Oral (51 patients)*
I term tent claudication	14	10
Marked improvement	6	2
Much improvement	4	2
Some improvement	2	3
Unchanged	2	3
Deterioration	0	0
Cerebral ischemia	7	7
Marked improvement	4	0
Much improvement	2	3
Some improvemen	1	4
Deterioration	0	0

among the comparative groups. As with the increased heart size their number was so small that tabulation would be meaning less.

Serum cholesterol

At the start of the study the total serum cholesterol of the 104 patients ranged from 213 to 411 mg per cent with an average level of 317 mg per cent per patient. There was no significant difference in the initial cholesterol decrease of 40 mg per cent or more that occurred in 31 patients receiving heparin whereas similar reduction was present in only 3 patients on oral therapy at the termination of the series. The greatest drop in both groups took place during the first month of therapy and in the patients with the highest initial cholesterol values. These values in the patients on heparin were more pronounced than those produced by a moderately low fat diet alone.[44] In approximately 80 per cent of the patients on oral anticoagulants the decrease in cholesterol was less than 20 mg per cent which corresponds to the reduction expected from moderate dietary restriction of fat alone

Electrocardiographic and ballistocardiographic tracings

Resting and poste ercise electrocardio- grams, as well as resting ballistocardio- grams were ecorded at specified times. The results at the start of the study and the effects of anticoagulant therapy are given in Table VII Special attention was paid to the S-T segments and T waves of the electrocardiograms since these were the portions of the tracings mainly affected by the therapeutic measures. When the elect ocardiogram was declared to be abnormal on the ba is of primary S-T segment and T wave changes these findings were d finite The presence of an abnormal postexer ise tracing was based on the more strict established criteria for interpretation of this test u The ballisto- cardiogram was declared to be abnormal by generally accepted standards, and these tracings were not specifically classi- fied as to deg ee of abnormality since this was not necessary for comparison Im provement in the electrocardiographic and ballistocardiographic tracings required def

Table IV The effect of anticoagulants on anginal pain in anginal groups

	Acute preinfarctional group		Chronic postinfarct anginal group	
	Heparin (25 patients)	Oral anticoagulant (24 patients)	Heparin (28 patients)	Oral anticoagulant (27 patients)
Angina pectoris				
Marked improvement	10	3	18	4
Much improvement	5	5	6	7
Some improvement	3	2	1	4
Unchanged	3	5	1	7
Deterioration	4	9	2	5

(5) deterioration—any decrease in effort tolerance or recurrent infarction.

The results of these monthly evaluations were summarized at the end of the study and are presented in Tables IV and V along with the average times when initial and maximal improvement occurred in these patients (Table V). Significant improvement occurred in all groups, but was greater in the patients on heparin. Not only was there a greater number of improved patients receiving heparin but their degree of improvement was also greater. In the patients with acute anginal pain who were receiving heparin 77 per

Table V The effect of anticoagulants on angina pectoris

	Type of anticoagulant	
	Heparin (53 patients)	Oral (51 patients)
Angina pectoris		
Marked improvement	28	7
Much improvement	11	12
Some improvement	4	6
Unchanged	4	12
Deterioration	6	14
Time of initial improvement		
Range	1-8 wk.	2-12 wk.
Average	3-4 wk.	6 wk.
Time of maximal improvement		
Range	1-10 mo.	3-18 mo.
Average	3-4 mo.	7 mo.

cent improved in comparison with 42 per cent improvement in the group of patients with acute angina who were on oral anticoagulants. The difference was even greater in the patients with chronic angina: almost 90 per cent on heparin improved as compared to 55 per cent improvement in the oral group. This demonstrates an 81 per cent improvement in patients receiving heparin as compared to an almost 50 per cent improvement in those on oral anticoagulants. Definite and persistent improvement in these patients had to be established before the data were included. Decreased consumption of sublingual nitroglycerin tablets quantitatively paralleled the amount of improvement.

Table V also demonstrates that the onset of definite and persistent improvement did not occur immediately but, in all groups, usually required a few weeks to become established. Transitory improvement was not considered. Heparin was somewhat more rapid in initiating the favorable response. Maximal relief of anginal distress required a few months of therapy in all patients. This relief was usually obtained in a shorter period with heparin.

Intermittent claudication and cerebral ischemia

Other clinical features of circulatory disorders such as intermittent claudication and transient cerebral ischemia were apparently benefited by the anticoagulants. Table VI depicts these effects in the two anticoagulant groups. Because of less exacting criteria for improvement and the

tient with larger lesions the pain and discomfort were severe enough to warrant discontinuation of the injections.

Four interesting side effects of heparin were noted. They were of minor significance since all were mild in degree and easily tolerated by the few patients involved. In the 2 diabetic patients on heparin there was a decreased requirement of insulin of 10 to 15 units, as has been observed by others.[43,44] The exact mechanism for this action is unknown. Alopecia of the scalp and brittle fingernails were two other side effects encountered that have been reported previously.[44] The alopecia was generalized and produced no cosmetic defect. Normal growth of hair returned when heparin therapy was stopped. The cause of these effects on epithelial structures is not known. Four patients complained of chronic musculoskeletal pain of moderate severity which involved various levels of the spine without demonstrating any clinical radiographic or laboratory evidence of possible etiology. No similar pain had been present previously and the symptoms subsided shortly after the heparin was terminated. To our knowledge similar or related symptoms have not been reported previously as being due to heparin itself. Pain in the back due to impurities in the heparin solution have been noted.[11]

Relative expense

The amount of heparin or oral anticoagulant taken by each patient was tabulated at monthly intervals. A similar tabulation was kept on the number of determinations of prothrombin time. Knowledge of the retail cost of the anticoagulants and laboratory tests was obtained and the expenses that would have been involved in the two therapeutic groups—had the patient borne the expense of the drug and of the test—were calculated and compared. The average retail cost of the laboratory test concentrated aqueous heparin U.S.P. 200 mg. c.c. bish-droxycoumarin tablets, 50 mg. and warfarin sodium tablets 5 mg. were used for the calculations. The relative expense of the average patient on heparin would have been approximately eight times that of the average patient on oral anticoagulant in this study. The expense of individual patients on heparin and those on oral anticoagulant will vary considerably depending on the amount of drug used, type of oral drug, number of determinations of prothrombin time, and various other factors.

Comment

Several factors were responsible for the different therapeutic groups being strictly comparable in this study. The clinical supervision, management, and therapy of the patients in each group, other than that of the anticoagulant drug, were the same during the study. The timing of the period of observation and its duration was similar in the groups. Selective discontinuation of therapy was also taken into account. These factors are of the utmost importance in such a study and have been emphasized.

The fact that the patients were not assigned in alternating fashion to the comparative groups may invite some criticism. This does not seem to be justified since the comparative groups were demonstrated to be well matched in many aspects (Table I). Exact matching of comparative groups is the cornerstone of establishing significant statistical differences.[44]

Although the comparative groups in this study were adequately matched, the wide variations in the natural history of this disease make possible a second criticism, i.e., that the number of patients involved may be insufficient to indicate valid results. It is true that large comparative groups are advantageous in this respect, but with prolonged observation smaller numbers of patients yield accurate information. The length of observation of these patients was adequate to obtain sufficient patient months on anticoagulation to demonstrate the superior effects of heparin in this situation.[11]

The combination of superior therapeutic anticoagulation and constant antilipemic action produced by heparin was presumably responsible for the results obtained in this study. It is difficult, if not impossible, to indicate which of these two major effects of heparin was more important. In this respect more emphasis needs to be placed on the possibility of the antilipemic factor being of equal or greater value since this

supports the concept that a fundamental metabolic effect important in atherosclerosis and its manifestation was being inhibited or corrected. This has been strongly supported by the studies of experimental and clinical reduction of myocardial oxygen uptake by hyperlipemia[64, 65] and the increased uptake with the clearing of hyperlipemia by heparin.[66, 6] Interference with oxygen diffusion has been proposed as the probable explanation for this decreased myocardial oxygen availability.[66]

Various effects of hyperlipemia are possible inhibitors of oxygen diffusion. The increase in blood viscosity,[7] adhesiveness and aggregation of erythrocytes[71] and blood cell agglutination may be factors.[72] Increased agglutination of blood cells (sludging) with hyperlipemia is significant, since sludged blood is a probable important hindrance to diffusion, particularly in smaller vessels.[72, 73] Other possible hindrances to oxygen diffusion by hyperlipemia are streaming of chylomicrons in plasma flow[66] and coating of red blood cells and vascular intima by the large lipid molecules.[74] A decreased rate of oxygen uptake by erythrocytes in hypercholesterolemic rabbits has been found.[75] It has been shown that diffusion through vascular walls is a function of molecular size and that with increasing molecular size there is decreasing diffusion. Deposition of fatty material upon the intima has been observed after several days of aortic perfusion. Triglycerides of hyperlipemic serum were shown to be unable to enter into the walls of excised arteries. Therefore, it is possible that interference with oxygen diffusion may result because the macromolecular low-density lipoproteins and chylomicrons form films on the intimal endothelium of vessels.[49] Because they reduce the permeability of capillary walls, the macromolecules of hyperlipemia form fat sludge on the intima, clog capillary pores, and thus mechanically interfere with the transmembrane passage of smaller molecules. After heparin therapy these macromolecules are greatly reduced by actual measurement, and the elimination of lipid films from the intima is indicated.[23, 4] Besides the increased uptake of oxygen by the heart muscle and other tissues that results from heparin therapy, the reduction of low-density lipoproteins and chylomicrons is probably important in retarding the rate of progression of atherosclerotic disease.

The amelioration of angina pectoris occurred in over 80 per cent of the patients who were treated with heparin, and it is noteworthy that the improvement was progressive over several months. The degree of improvement was particularly striking. A serious limiting factor in studying angina pectoris has been the demonstration that placebo therapy has been effective in 25 to 40 per cent of the patients,[7] but this could not explain the results in 80 per cent. Unpredictable improvement without any therapy of the angina syndrome has been noted, but in less than 50 per cent of the cases.[7] Continuous long-term oral anticoagulation has been reported to produce progressive improvement in almost 50 per cent of anginal patients after 1 year of therapy. These results are not significantly different from those obtained with oral therapy in this study. Prolonged intermittent heparin therapy for 2 years produced 50 to 75 per cent improvement in angina, and this improvement was also progressive over several months.[14] Other studies that interchanged intermittent heparin and placebos at intervals of several weeks in angina patients reported no improvement.[64] The longest study was about 1 year, with the others being less than 6 months. The conflicting reports on the value of heparin in angina cannot be adequately explained. The length of heparin therapy and the differences in patient material may be partly responsible.[64]

The significant lowering of serum cholesterol in almost 60 per cent of the patients receiving heparin has not been reported previously. It has been held that heparin has no influence on serum cholesterol. However, plasma levels of endogenous heparin in normal individuals have an inverse relationship with serum cholesterol and low-density lipoproteins.[46] This would seem to indicate that the action of heparin on serum cholesterol varies from patient to patient.

The improvement in the electrocardiographic and ballistocardiographic tracings provided the objective evidence that corresponded with the subjective clinical

benefits and probably represents enhanced myocardial oxygen uptake and return toward normal tissue function.

The possibility that subjective improvement in anginal pain may have been related to the psychological effect of parenteral therapy as compared to oral therapy cannot be excluded with certainty. However, it is very unlikely that such an effect could have been responsible for the differences observed on the basis of several objective criteria including mortality and infarction which have been mentioned.

Patients with previous myocardial infarctions and severe angina pectoris may benefit significantly from several months of continuous or intermittent heparin therapy. In view of the expensiveness of heparin for continuous use over a long period of time, it may be that the most practical plan would involve the continuous long term use of oral therapy with intermittent injections of heparin two or three times per week. This may be the most rewarding regimen in clinical atherosclerosis with or without demonstrable hyperlipemia.

To our knowledge, this is the first published study on continuous long term heparin therapy in patients with angina pectoris. Results reveal that this method of anticoagulation is feasible, safe and highly beneficial in clinically severe advanced coronary artery disease.

Because of the absence of a control group of untreated patients, this study offers no data in regard to the value of long term oral anticoagulants.

Summary

1. Two matched groups of patients with severe coronary artery disease manifested by Grade III-IV angina pectoris and one or two previous "poor risk" myocardial infarctions, were treated continuously with anticoagulants. 53 patients with concentrated aqueous heparin subcutaneously and 51 patients with oral medication for a total period of 2,299 patient months with the average duration of therapy being 22 months per patient.

2. Among the patients on heparin there were 3 deaths (5.6 per cent) and 6 recurrent infarctions (11.0 per cent) in contrast to 8 deaths (15.7 per cent) and 14 recurrences (27.5 per cent) in the patients on oral anticoagulants.

3. Definite progressive improvement of the anginal syndrome occurred in 43 patients (81 per cent) receiving heparin in contrast to improvement in 25 patients (49 per cent) on oral therapy. The degree of improvement was also strikingly greater with heparin.

4. Periodic electrocardiograms, ballistocardiograms, and electrocardiographic exercise tests demonstrated progressive improvement of about the same frequency and degree in the two anticoagulant groups as that which occurred in the anginal syndrome of these groups.

5. Total serum cholesterol had a persistent decrease of over 40 mg. per cent in 31 patients on heparin (58.5 per cent). Cholesterol was much less reduced in patients on oral therapy.

6. The probable reasons for the superior therapeutic effect of heparin over prothrombin-depressing drugs were stated.

7. A possible mechanism for the increased myocardial oxygen uptake produced by heparin was discussed.

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Experimental
and laboratory reports

"Aimed" electrocardiography
Model studies, using a heart consisting of 6 electrically isolated areas

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The electromotive forces of the heart are recorded in one of three ways: (1) by most currently used electrocardiographic and vectorcardiographic leads as a variable and unknown mixture of dipole contributions from all parts of the heart[1-4] (2) by some recent orthogonal leads[-4] as a sum of approximately equally weighted over all dipole contributions and (3) by "null" leads[5,6] as a sum of dipoles from the heart as a whole with the exception of a limited null area. In a previous report[7] it was shown that a *fourth* type of lead select vely sensitive to dipoles in a limited cardiac area but insensitive to dipoles in *other* areas referred to as an "aimed" lead is a theoretical possibility. The purpose of the present paper is to describe an electrocardiographic lead system which approaches this type of recording in a three-dimensional heart torso model.

Using a solid three-dimensional heart model within a torso-shaped electrolytic tank, the reciprocity theorem will be applied to determine the dipole strengths of isolated cardiac areas. Potentials are measured at eight electrodes on the torso surface after each area has been excited separately in turn. After all cardiac areas have been excited to different strengths, and the corresponding surface voltages have been measured again, it is then possible to calculate the area dipole moments by the solution of a set of simultaneous linear equations for each set of surface measurements. In actual use these calculations are automatically computed by a tapped resistor network which records the lead.

Green's theorems. The theorems of the Cambridge mathematician George Green[8] (1828) are fundamental in electrostatic theory[9] and have recently been applied in electrocardiography. They are generally expressed in voltages and charges in dielectric media, but can also be applied to voltages and currents in conducting media: current replaces charge, and conductivity replaces dielectric constant. A special application of Green's reciprocity theorem by Helmholtz (1853) to electrophysiology, involving currents and voltages, is the basis of the important McFee-Johnston lead field concept.[1] Green's theorem of equivalent strata was used[2,11] to determine the dipole moment of the heart and also as an alternative to the single equivalent dipole hypothesis.[3] Two further applications of the reciprocity theorem appear in the present paper.

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The measurement of specific dipole regions within the heart

If it is assumed that there are N dipole regions in the heart, then it is possible to make an electrolytic tank analogue of homogeneous conductivity enclosing a heart model of higher conductivity on which the dipoles would be represented by many pairs of closely spaced current sources and sinks. Obviously this model would be difficult to construct, and one would settle for one resultant dipole in the center of each region of interest.

If N electrodes are now distributed over the surface of the torso model, it is possible to measure N sets of N potentials as each of the dipole regions is excited in turn. Alternatively, if all of the N dipole regions are excited to different strengths simultaneously and N potentials are measured in the same positions on the torso surface then it is possible to calculate *the strengths* of each of the N individual dipoles by solving N simultaneous linear equations. The coefficients in the equations are obtained from the N×N set of potentials described above. The solutions to the equations give the dipole strengths which appear in the form

$$\mu_a = c V + c V + c V + c V + \quad + c_N V_N$$

where V, V_2, V_3, etc. are the body surface potentials measured relatively to the potential of a reference electrode (see Equation 6 below). Thus, there will be N+1 electrodes in all.

The main objections to this concept are the difficulty in manufacturing a homogeneous heart of finite conductivity and inadequate representation of dipole regions by one resultant dipole in each. Both of the objections can be overcome by an application of Green's reciprocity theorem which makes it possible to measure the strength of each of the N dipole regions by applying currents at each of the N points in turn on the body surface and measuring the average fields over each of the regions. It is assumed that the dipole strength is uniform over each of the regions considered. For example, if a dipole region is excited to a strength μ_a, and this produces a potential V at a point on the body surface (relative to the reference electrode) then a current I injected at the surface point will produce an average electrical field over the dipole region of strength E_a, where μ_a, I_1, E_a, and V_1 are related by

$$\mu_a = \frac{I_1}{E_a} V \tag{1}$$

E is the field component acting parallel to the dipole force at any point (Fig. 2,A). Thus all the information required to measure N sets of N potentials as each dipole is excited in turn can be obtained by performing an experiment in which currents are injected on the surface and electrical fields are measured over the heart.

The average electrical field over each region is not easy to measure for the case of a heart of finite conductivity. With a heart of infinite conductivity, however, the surface can be subdivided into areas, each separated electrically from the others, in which case the surface field is simply proportional to the current arriving on each, that is,

$$E_a = \frac{I}{A} \tag{2}$$

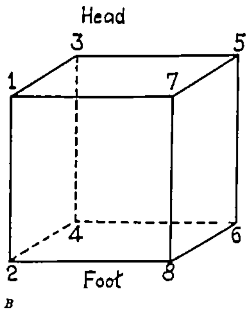
where I is the current arriving on region "a," and A is its area, is the conductivity of the medium surrounding the heart. In this case, of course, the electrical field can only exist perpendicular to the surface of the heart. The method is most accurate if the direction of dipolar action is in the same direction as the electrical field. It is not known how far deviations from this dipole arrangement will affect accuracy in vivo.

In reality, a heart of infinite conductivity cannot exist; hence, a correction must be made to allow for this. It is shown in the Appendix that if the conductivity of the heart is 4 times that of the surrounding medium, then the actual field acting perpendicular to the high conductivity region is given by

$$E_a = E \times 0.73 \text{ approximately} \tag{3}$$



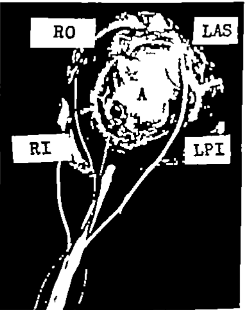
A



B



C



D

Fig. 1. *A*, Torso-shaped tap- ter filled, fiber-glass tank, shielded with aluminum foil. Eight metal screws, corresponding t the Z lead of the SVEC III lead system, serve as electrodes. *B*, N mbering of electrodes for T ble I. *C*, Cast of four cardiac chambers of healthy heart. *D*, Left anterior iew of completed heart model. By dipping the cast in ax its olume was brought to pproximate the heart in partial trial ystole and ventricular diastole as during the inscription of QRS. The surface was then coated with foil and, by removing 2-mm. trips of foil, divided into six areas: *A* pical; *LAS*, *LPI*, left entricular anterosuperior and left entricular posteroinferior; *RI*, *RO*, right ventricular inflow and right entricular outflow tracts; and *atrial*, which in this iew ppears as rim surrounding the entricles.

bnorm l t es i th st undard electrocardio r i n

Right ventr cular hypert ophy Right ven tri ular hypertr phy was present in too few of the standard tracings to permit eval u ition

Atrioventricular and bundle branch blocks (*Fig 3 4 6*) All 26 tr i ings which showed complete left and right bundle branch blocks were read as abnormal or sus picious l abnormal Although incomplete right bundle branch block was generally n t difficult to recognize it was considered to be too insignificant to warrant referral Three of four intraventricular conduction defects without infarction were diagnosed by the oblique lead

Atrioventricular conduction defects gen erally were easy to recognize Nineteen of 24 tracings which showed first-degree atrioventricular block were read as abnormal or suspiciousl abnormal by the oblique lead In retrospect all but one of these should have been recognized

Atrial a hythmias and atrial hypertrophy (*Fig 3 and 6*) Thirty-seven of 41 atrial arrhythmias were recognized Four ar rhythmias including 3 cases of atrial fibrillation were missed primarily because of th short length of the tracings.

Three of 6 tracings (50 per cent) which showed trial hypertrophy alone were read as bnormal or suspiciously abnormal by the ingle lead because of increased ampli tude or breadth of the P wave The tracings missed showed borderline changes which with more experience we might easily have been able to read as suspiciously abnormal

P imary T wave changes (*F gs 3 5 and 6*) Primary T wave changes without other abnormalities were seen in 66 tracings. Forty-one (4 per cent) were read as abnormal or su picious ly abnormal by the obl que lea l Generally T wave changes seen only in Leads V_5 and V were not recognized in the single lead Some of these changes in the standard tracing may have been due to electr le position Minor T wave abnormalities such as flattened T waves in Lead V_1 and V_4 accounted for most of the other mi sed abnormalities

Miscellaneous Low voltage prolonged Q T interval and recurrent ventricular extrasystoles were recognized in 21 of 23 in stances in the single-lead electrocardiogram

Comparison with Lead I

One hundred and forty nine of the 176 abnormal complete tracings (sensitivity rate 85 per cent) were interpreted as abnormal or suspiciously abnormal from Lead I alone in Survey Group 1 Of 121 normal tracings only 86 tracings (specificity rate 71 per cent) were read as normal by Lead I This results in a rate of overreferral two and one-quarter times that of the oblique lead If only definitely abnormal Lead I tracings were referred the specificity rate would rise to 94 per cent but the sensitivity rate would fall to 66 per cent so that a significant number of electrocardiographic abnormalities would be missed From Lead I alone 79 per cent of the infarcts might have been suspected however the speci ficity rate of 71 per cent would make the number of overreferrals almost prohibitive

Discussion

Detection of electrocardiographic abnormalities should provide evidence of heart disease which would be unsuspected by other means. Surveys on selected small populations with the complete electrocardiogram have yielded a surprisingly high incidence of abnormalities indicative of significant disease.[3-6] For surveys of large populations the use of the complete elec trocardiogram would be impractical except in unusual circumstances.[7] Other types of screening techniques using an abbreviated electrocardiogram or special leads which result in a considerable saving of time have not proved practical because of low sensitivity and/or low specificity rates. [8-11] The oblique lead described here is capable of detecting a large number of abnor malities presumably because of its relationship to the horizontal vertical and sagittal components of the heart s electromotive force With experience we have been able to attain sensitivity and speci ficity rates approximating 90 per cent with this lead Exact evaluation was not possi ble because of the number of standard elec trocardiograms which showed equivocal or only suggestive fin l ngs which might have been interpreted differently by other observers. F r thi re son each laboratory should determine its own set of normal values for the ol lique le l

Advantages of the single oblique screen

Here again it is assumed that the dipolar effect is always normal to the surface Although in the heart the dipole layers exist a short distance outside the high conductivity surface the field there is assumed to be not much different from the field on the surface This assumption will be valid if the dipole layer is close to the endocardial surface, as compared with the *radius of curvature at any point.*

The current I does not have to be measured directly if one again applies Green s reciprocity theorem If a region of the infinitely conducting heart is raised to a potential V above the remaining N 1 regions short circuited together as shown in Fig 2,*B* and this produces a potential V at a body surface point, then a current I injected at the body surface point would produce a current I on the same heart region where

$$I = I \quad \frac{I}{I} \tag{4}$$

Combining Equations 1 2,3 and 4 the expression relating dipole strength and body surface potential becomes

$$\mu_a = \frac{I_1 \; 4}{0.73} \quad \frac{I}{I} \tag{5}$$

It is thus possible to establish the NXN set of simultaneous equations by simply performing an experiment in which each heart region is raised to a potential V' in turn and measuring the N resulting body surface potentials in each case i.e.

I I I I

Hence if all d polar regions are excited simultaneously we obtain the following set of N

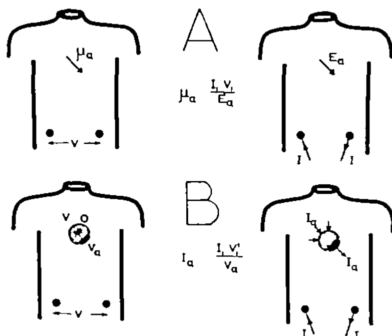


Fig 2 *A* This pplication of Green reciprocity theorem replaces measurement of dipole moment by measurement of field trength See Equation 1 in text. *B* Applying the theorem again in another form, the experiment is reduced to measurement of current nd oltage See Equation 4 in text.

equations for the resultant potential at each of the body surface electrodes relative to the reference potential (matrix notation has been used)

$$V_i = k_{ij} \mu_j \qquad i = 1, 2, \ldots N; \quad j = a, b, \ldots N$$

$$\text{where } k_{ij} = \frac{0.73}{\sigma_1} \cdot \frac{I_i}{I_{ij}}$$

The set of N equations must now be solved by standard computer techniques so that the values of the required dipole moments appear as functions of the electrode potentials. In other words μ_a, μ_b, μ_c, etc. can be expressed as linear combinations of the body surface potentials with appropriate numerical coefficients, e.g.

$$\mu_a = c_1 V_1 + c_2 V_2 + c_3 V_3 + \ldots + c_N V_N \tag{6}$$

It is better to evaluate the ratios μ_a/A_a, etc., since these quantities do not vary with body size and therefore permit the solutions for one size of torso to be generally applicable to any other, provided that scale alone changes. The fractions of the various body surface voltages which must be added to give dipole moment per unit area are given in Table I,a-c.

Approximations and errors in the model

The accuracy of model studies is limited by our relative ignorance of the electrical and some of the relevant anatomic properties of the torso and the heart, the difficulty of reproducing in the model what is known, and the fact that a model can be no better than the mean of many variables. The clinical applicability of the present method will be affected by in vivo variation in the position, shape, volume, and conductivity of the heart, in the relative size, shape, and conductivity of the torso, and in the distribution and orientation of the intramural dipoles.

The model heart used in this study represents intracardiac blood in partial atrial systole and full ventricular diastole as found during the inscription of the QRS complex.[13] The volume of the heart corresponds to reported fairly unanimous anatomic, radiologic, and cineangiographic data,[14] while the position of the interventricular septum and the relative positions of the two ventricles correspond to published anatomic[14,1] and angiographic[19] findings.

Radiologically determined, the frontal plane axis of the heart ranged from 22 to 54 degrees in adults[22,23] and from 15 to 95 degrees in children with congenital cardiopathy.[24] Accordingly, the model was investigated with the heart in a horizontal, intermediate, and vertical position (Table I). On the other hand, Grant's[15] and Walmsley's data induced us to make at this stage no correction for the apparently rather slight rotation around the long axis of the heart. No correction was made so far for cardiac rotation around the long axis of the body, and for changes in the location of the heart within the chest.

Apart from the high-conductivity area of intracardiac blood, represented by the metal coating of the heart model, the conductivity of the torso analogue was homogeneous. The reasons for this were given before.[3]

With regard to intramural dipoles, four, only approximately correct, assumptions were made: that each dipole is perpendicular to the endocardial surface, that the dipoles form a continuous layer, and that the dipole layer is parallel to, and at a negligible distance from, the endocardial surface.

Reduction of error with additional electrodes. If there are more than N+1 electrodes on the body surface where N regions are under investigation on the heart, then it is possible to use the additional information to improve the accuracy and render the results less susceptible to changes in cardiac rotation and position and to departures in torso shape and conductivity from the original model. The method involves forming the normal equations of least squares,[25] which constitute a set of N equations with N unknowns. The information from the various body electrodes can also be statistically weighted if it is suspected that some points are less reliable than the others. In experiments performed to date, 5 ventricular

Table I Factors used when adding body surface potentials to give dipole moment per unit area (amperes per centimeter)

Area	I	I	I	I	F	I	I
( ) *Anatomic axi of heart +15°*							
A	+ 0144	− 0090	+ 0108	+ 0083	− 0010	− 0110	+ 0096
LAS	− 0315	+ 0003	− 0255	− 0275	− 0205	+ 0456	− 0033
LPI	+ 0187	+ 0054	+ 0277	+ 0521	+ 0670	− 0400	− 0010
RI	− 0711	+ 0157	− 0521	− 0459	− 0088	+ 0540	− 0045
RO	+ 0248	+ 0259	+ 0173	+ 0229	+ 0217	− 0191	+ 0005
(b) *Anatomic xis of heart +45°*							
A	− 0011	− 0027	− 0007	− 0028	− 0045	− 0018	+ 0055
LAS	− 0054	− 0035	− 0010	− 0011	− 0049	+ 0241	+ 0008
LPI	− 0097	+ 0143	− 0039	+ 0278	+ 0755	− 0158	− 0027
RI	− 0231	+ 0010	− 0137	− 0218	− 0188	+ 0148	− 0022
RO	+ 0149	+ 0327	+ 0049	+ 0197	+ 0361	− 0098	0
( ) *Anatomic axi of heart +70°*							
A	+ 0143	− 0206	− 0015	− 0078	− 0094	− 0182	+ 0110
LAS	− 0377	+ 0067	− 0150	− 0191	− 0175	+ 0460	− 0021
LPI	− 0119	+ 0115	+ 0153	+ 0482	+ 0606	− 0233	− 0041
RI	− 0286	+ 0006	− 0195	− 0341	− 0326	+ 0262	− 0091
RO	+ 0038	+ 0477	+ 0179	+ 0450	+ 0499	− 0182	+ 0025

The figures apply strictly only to the model studied The errors involved when using another model, or in the living heart, are unknown. Areas: *A* apical *LAS, LPI* anterosuperior and posteroinferior left ventricular *RI RO* right ventricular inflow and outflow tracts. V V 3 etc. Body surface potentials measured relative to the potential of the reference electrode No 4 *1 to 8* Electrode numbers as in Fig ,B.

regions ha e been considered and 8 body electrodes used. One of the electrodes, however is the reference electrode so that there are two excess sources of information. Six electrodes were equally weighted and the seventh nearest the heart by the apex, was given a statistical weight of one half since t was thought that this could contribute large errors if the heart was positioned differently from the position used in the torso. It is considered that a much larger number of body electrodes is desirable except for the added burden of attachment and calculation

Switchbox resistor networks

In practice the linear combinations of voltages in Equation 6 are performed by a series of potentiometers, each one joining the body surface electrode to the reference electrode and subdivided according to the coefficients c c c c etc (Fig 3,B) If the coefficient is positive the tapping point is connected to the positive terminal of an electrocardiograph and if negati e, to the negative terminal. Therefore, the wa eform should represent that due to the specific dipole region chosen with an appropriate scale factor to give the actual trength in amperes per centimeter for μ/A. The potentiometers are set according to the factors in Table I,a-c It is desirable to scale up the factors so that for any particular measurement the largest number is made to correspond to a maximum potentiometer setting this gives useful output voltages. The maximum potentiometer setting does not gi e exactly 100 per cent of the surface voltage if the skin resistance is appreciable for example with 50-kilohm potentiometers and a skin resistance of 1,500 ohms the maximum sett ng corresponds to 97 per cent of the full available voltage at that point. The 220-kilohm resistors in the slider circuits are switched accord ng to the signs of the factors in the table and in cases in which several of them meet the voltage at that point is divided by the number of branches. For example If 4 resistors are switched to the positive terminal and the other 3 to the negati e terminal then the negative voltages must be reduced on the potentiometers by a factor $^3/_4$ to achieve balance and the voltage recorded will only

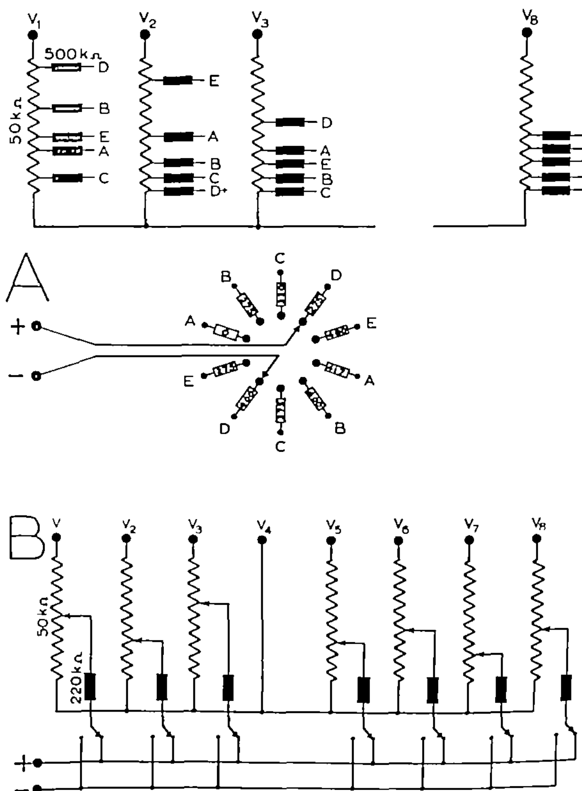


Fig. 3. Networks used for combining body surface potentials through dipole moments from selected areas. *A*, Example of switched 5-position network, long axis of heart is 45 degrees. *B*, Continuously variable network. Abbreviations: *A*, apical; *B,C*, anterosuperior and posteroinferior left ventricular; *D,E*, right ventricular inflow and outflow areas. [illegible] Body surface potentials measured relatively to the potential of the reference electrode No. 4. *1-8*, Electrode numbers as in Fig. 1,*B*.

$^1\!/_4$ of the true voltage. If the potentiometer settings have been scaled up this factor must also be taken into account if a quantitative result is required

Fig 3,*A* shows how the continuously variable network can be converted to a form whereby the five measurements can be selected by a single switch The principles are the same as above, except that a higher value of resistor (500 kilohms) is used for all the tapping points. This could lead to a relatively variable output impedance when used with an electrocardiograph of 3-megohm input impedance. To avoid this difficulty a resistor has been placed in series with each of the junctions A+ B+ E− so that the same impedance of 500 kilohms is always presented to each of the terminals of the electrocardiograph this will then introduce a constant-scale factor All impedances in the above are measured between ground and the point of interest since the body is normally earthed. The network n Fig 3,*A* illustrates how Table 1,*b* might be used Table I,*a* and *c* would have to have separate networks, and to avoid undue loading the body electrodes should be switched to the chosen network rather than remain connected to all three

The right lower dorsal electrode was chosen as a reference electrode since it is most likely to be approximately at the mean potential of all the others, so that little current flows, thereby reducing errors due to a drop in voltage across skin resistance. All other electrodes have 50 000-ohm potentiometers connected so that skin resistance is relatively unimportant, although t can still be taken into account if extra accuracy is desired The voltages recorded in man using these switching networks are lower than those yielded by the conventional electrocardiographic leads, and a Sanborn amplifier with fivefold sensitivity will be used in further studies.

Summary

With the exception of the McFee Johnston null leads the voltages n electrocardiographic leads are due to synchronous electromotive forces all parts of the heart. This applies to bipolar and unipolar conventional leads and to all available orthogonal and vector cardiographic lead systems

Aimed electrocardiographic leads, on the other hand are defined n the present paper as responding to electromotive forces in a limited cardiac area, while being insensitive to forces in other regions of the heart

A three-dimensional model of the human torso and the heart was built The model heart was a cast of the 4 cardiac chambers. In the living heart, intracardiac blood represents a region the conductivity of which is finite homogeneous, and higher than that of the torso whereas, for reasons stated the heart model consisted of insulating material with a surface coating of infinite conductivity The coating was divided by nonconducting strips, into 1 atrial and 5 ventricular areas. The torso was otherwise homogeneous. Eight brass screws, representing electrodes placed as in the Z lead of the SVEC III lead system penetrated the wall of the torso.

A method for calculating the dipole moment of each of the cardiac areas, from the voltages appearing at the 8 electrodes, is given n detail

A simple network which automatically performs the calculations, and thus is able to supply a standard electrocardiogram with voltages due to each of 5 ventricular areas, is described

Some discrepancies between the model and the living heart which are likely to cause errors that impair the clinical usefulness of the method are listed and means of reducing error are discussed

Appendix

The electrical field near a model heart of finite conductivity It is desired to calculate the electrical field normal to the surface of an irregular body having a conductivity k relative to the surrounding medium The electrical field is composed of two parts, one due to the external generating source and one due to the electrical images induced in the body The image field may be regarded as perturbing the field E which exists in the absence of the body or when k = 1 The perturbations tend to zero as k tends to unity

If the body is an infinite plane the image field due to an external charge is proportional to $\frac{1-k}{1+k}$ and similarly for an infinite cylinder.[9] The heart however approximates more closely a spherical body so that it is of interest to investigate that particular case. The radial field due to the images of an external charge is found to be[24]

$$E = e(k-1)\sum \frac{(n+1)}{k+\left(\frac{n+1}{n}\right)} \quad \frac{a^{+}}{b^{+} r^{+}} \quad P(\cos\theta)$$

where b is the radius of the external charge +e from the center a is the radius of the sphere and r is the radius at which the field is measured. The angle θ gives the direction in which the field is measured relative to a line joining the external charge to the center of the sphere. Hence

$$E > \frac{k-1}{k+2}\sum \frac{e\ (n+1)\ a^{2n+}}{b^{+}\ r^{+}} \quad P(\cos\theta)$$

and

$$E < \frac{k-1}{k+1}\sum \frac{e\ (n+1)\ a^{2n}}{b^{+}\ r^{+}} \quad P(\cos\theta) \tag{7}$$

The total radial field just external to the heart surface may therefore be expressed as

$$E > E + B\ \frac{k-1}{k+2}$$

where B is the sum of the series in Equation 7

$$E < E + B\ \frac{k-1}{k+1} \tag{8}$$

The above inequalities assume that the conductivity k is greater than unity. If k is smaller than unity the image field is reversed necessitating a reversal of the inequalities.

Now consider the following two cases

$$(1)\ \text{if } k = 0 \quad E_{0} = 0 < E - \frac{B}{2}$$

$$0 > E - B$$

since the field perpendicular to the surface of the sphere can only be zero.

$$(2)\ \text{if } k = \infty \quad E_{\infty} = E + B$$

Using these inequalities it is now possible to show from Equation 8 that for any conductivity k between unity and infinity the radial electrical field near the surface of the sphere lies between the following limits

$$\frac{E_{\infty}}{2}\left(1+\frac{k-1}{k+1}\right) > E > \frac{E_{\infty}}{3}\left(1+2\ \frac{k-1}{k+2}\right)$$

The resistivity of the blood in the heart was found to be roughly 100 ohm cm[22] whereas that for the remainder of the body is approximately 480 ohm cm.[23] Hence if k is taken equal to 4

$$0.80\ E_{\infty} > E > 0.66\ E_{\infty}$$

i.e. $E = 0.73\ E_{\infty}$ with an error smaller than about 10 per cent

The method for calculating the field normal to the surface of a conducting heart (k = 4) then reduces to the measurement of the field over a small area on the surface of a perfectly conducting heart (k = ∞) and multiplication of the result by 0 73

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Premature narrowing or closure of the foramen ovale

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Premature narrowing or closure of the foramen ovale is an infrequent but not rare anomaly. We have found 25 cases reported in the literature, the details of which are presented in Table I.[1-21] Analysis of 1,150 cases of congenital heart disease studied at the Congenital Heart Disease Research and Training Center revealed 10 examples of this anomaly.

This is a report of the pathologic anatomy in these 10 cases as studied quantitatively by a method previously reported.[22] In addition, this is a clinical-pathologic study of one case in which the diagnosis was strongly suspected clinically.

Materials and methods

In all cases a thorough gross study of the heart, including valves and endocardium, was made. Seventeen modalities were measured, including total heart weight, thickness of walls, sizes of chambers and sizes of orifices, and in one case weights of the parietal wall of the ventricles. When body height and weight or either of these were known in addition to age, the normal values for individuals of such age, height, and/or weight and the 5 per cent range of confidence were computed from the formulas previously presented.[22] When only age was known, the normal values were read directly from the curves, using age as the independent variable.[22]

Judgments of hypertrophy and dilatation of ventricles and sizes of orifices were thus made with the concept of a trend in a number of cases rather than absolute positivity or negativity in any one individual case. In an individual case, only if the value fell outside the range of the 5 per cent level of confidence was it considered to be definitely abnormal. Otherwise the statement above or below the mean was used. The atria were judged only qualitatively. In Case 31, a thorough clinical evaluation was made and, hence, a clinical-pathologic correlation is presented as a prototype of this complex.

From the Congenital Heart Disease Research and Training Center, Hektoen Institute for Medical Research; the Department of Pathology of the Presbyterian-St. Luke Hospital, Northwestern University Medical School, and the University of Chicago School of Medicine; the Cardiophysiology Department, Cook County Children's Hospital; and the Loyola Psychometric Laboratory, Loyola University, Chicago, Ill.
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Analysis of cases in literature and our 10 cases

The cases in the literature may be divided into three groups (1) those without ventricular septal defect and without mitral atresia (19 cases) (2) those with ventricular septal defect but without mitral atresia (3 cases) (3) those with mitral atresia (3 cases) Our 10 cases consist of 4 cases of Group 1 and 6 cases of Group 2. We also have a case of premature closure with mitral atresia but in view of the fact that a levoatriocardinal vein was not found by the prosector it is not being reported The anatomic details of these cases are presented below Other data in regard to these cases are presented in Table II

A Premature narrowing or closure without mitral atresia or ventricular septal defect (Figs 1 and 2) Cases 513 1017 1047 and 1095

EXTERNAL ANATOMY OF THE COMPLEX. The heart was enlarged in its transverse diameter with or without an increase in total heart weight. The apex was formed by the right ventricle alone with the left ventricle slightly sharing in the apex occasionally The pulmonary trunk and aorta were in their normal position with the pulmonary trunk larger than normal and the ascending aorta small or minute A large left atrial appendage was apparent in 2 cases.

INTERNAL ANATOMY OF THE COMPLEX. All cases in our series were associated with mitral stenosis and aortic atresia. The right atrium was hypertrophied and dilated and there was a tendency for the right ventricle to be similarly involved. The endocardium of the right atrium was hypertrophied whereas that of the right ventricle was normal or focally or diffusely hypertrophied. There was a tendency for the tricuspid and pulmonary orifices to be enlarged with increased hemodynamic changes in their valves. The left atrium was small with a thick wall and in some cases with an enlarged left atrial appendage, and with marked hypertrophy or frank fibroelastosis of the endocardium The mitral valve consisted of short often thickened leaflets with short chordae and short stubby papillary muscles. The left ventricle consisted of a minute chamber that had a tendency toward a thick wall with marked endocardial fibroelastosis. The ascending aorta was a minute vessel which proceeded to the base of the heart and ended blindly giving off the coronary arteries at the blind end. The transverse aorta was larger than the ascending portion but smaller than normal. The ductus arteriosus was widely patent. In one case the right upper pulmonary vein entered the right atrium In another the left subclavian artery was given off at the point of entry of the ductus.

B Premature narrowing or closure of the foramen ovale with ventricular septal defect without mitral atresia (Figs 3 and 4) Cases 31 413 491 557 833 and 1143

EXTERNAL ANATOMY OF THE COMPLEX In most cases the heart was enlarged, and in some cases it was increased in weight. The apex was usually formed by both ventricles, less commonly only by the right. The aorta and pulmonary trunk appeared to be in their normal position externally with the aorta smaller than the pulmonary trunk, but not so small as in the previous group.

INTERNAL ANATOMY OF THE COMPLEX. In all 6 cases the ventricular septal defect was large and of a characteristic type. It was situated in the place of the pars membranacea and involved the anterior and posterior septa adjacent. The defect was confluent with the mouth of the aorta, which overrode the septum. In 2 cases there was a second defect in one of these it was in the posterior septum at the base and in the other it was in the more apical part of the ventricular septum—the sinusoidal type seen only microscopically Accompanying the defects in all cases was an abnormality in the configuration of the left side of the ventricular septum with various thick trabeculae

The right atrium was hypertrophied and dilated with diffuse endocardial hypertrophy The right ventricle had a tendency to be hypertrophied and dilated with or without endocardial hypertrophy The tricuspid and pulmonary orifices were in most cases enlarged but occasionally the pulmonary orifice was normal in size. The tricuspid and pulmonary valves showed generalized increased hemodynamic change with an additional focal hemodynamic change in the tricuspid valve related

Table I. Premature narrowing or closure of foramen ovale. Review of literature

Author, year	Age	Foramen ovale	Fossa ovalis	Left heart chambers	Fibroelastosis	Other findings
A. Without Ventricular Septal Defect or Mitral Atresia						
Vieussens 1715	36 hr	Closed		?	?	Pulmonary congestion
Smith, 1846-8	21 hr	Closed	Present	Small	Left ventricle	Mitral and aortic stenosis
Tai 1875	Minutes	Narrow	?		?	?
Osler 1880	Stillborn	Narrow	Present	Small	None	Mitral stenosis
Lehman, 192	32 hr	Closed	Absent	Small	Left ventricle	Deformed aortic valve
Bellet and Gouley 1932	12 hr	Closed	Present	Small	Left ventricle	Hypoplastic mitral valve, aortic atresia, accessory vein from left atrium possibly connected to superior vena cava
Reid and Krumbhaar 1932	Stillborn	Closed	Present			?
Benner (Case 1) 1939	Stillborn	Narrow	Present	Normal	None	—
Benner (Case 2), 1939	11 hr	Narrow	Present	Normal	None	Marked pulmonary congestion
Patten, 1938	1 mo	Narrow	Present	Hypoplastic		?
Raeburn 1951	Few min.	Narrow	Present	Hypoplastic	?	Large left diaphragmatic hernia
Wilson et al (Case 1) 1953	36 min.	Closed	Absent	Small	?	Aortic stenosis, left diaphragmatic hernia
Wilson et al (Case 2), 1953	4 hr	Narrow	Present	Normal		Pulmonary congestion
Kreutzer and Vaillac 1942	16 hr	Closed			?	Pulmonary congestion
Brody (Case 1) 1953	46 hr	Narrow	Absent	Relatively small		Pulmonary congestion
Gresham, 1955	3 hr	Closed	Absent	Small	Left ventricle	—

*Unless otherwise specified, the right heart chambers are hypertrophied, the pulmonary trunk is dilated, and the ductus arteriosus is patent or widely patent. Table I is continued on p. 641.

to the ventricular septal defect. The pulmonary trunk was larger than normal. The left atrium was small with a thin wall and normal or thinned endocardium. The mitral orifice was either large or small but not stenotic in the sense of that present in the previous group. The aortic leaflet of the mitral valve showed in some cases increased hemodynamic change. The left ventricle had a tendency to be somewhat smaller than normal and its wall was somewhat thinner than normal. Its endocardium

ing lead are only two electrodes need be applied the breast area is avoided the subjects need not disrobe the electrodes can be placed uncritically and electrocardiograms can be obtained with the subject in a sitting position The disadvantages of the posterior axillary placement of the back electrode was solved easily by fabrication of the halter shown in Fig 1 However suction cup electrodes have been used without difficulty except in women wearing tight outer garments.

The oblique chest lead was tested primarily to determine its usefulness as a screening device in large populations since 30 to 50 subjects can be screened hourly with this technique. However several other possible uses are suggested First this lead might be substituted for the complete electrocardiogram in annual or periodic industrial or employee health examinations. This was tried on a small scale on employees of the Oklahoma State Department of Health on the initial examination a complete electrocardiogram and a single oblique chest lead electrocardiogram were obtained one year later the single-lead electrocardiogram was repeated with the intention of obtaining a complete tracing on those persons who showed any change Only 1 of 34 such tracings showed an appreciable change and this was confirmed by a corresponding change in the complete electrocardiogram Most repeat tracings were identical or nearly identical with the initial one. The single, oblique chest lead should prove useful in recording the electrocardiogram during exercise These studies are now in progress. Its usefulness in screening children for electrocardiographic abnormalities is also being evaluated Finally this lead would appear to be adaptable to programming for rapid computer screening of electrocardiograms

Summary

Single, oblique chest lead electrocardiograms from 996 subjects have been compared with standard electrocardiograms in order to test the efficiency of the single lead as a screening technique Tracings were obtained from hospital patients, small selected groups of subjects, and a large institutional population. The oblique chest lead was effective in demonstrating myocardial infarction left ventricular hypertrophy arrhythmias, atrioventricular and bundle branch block atrial hypertrophy and primary T wave changes. Its over-all specificity was 87 per cent with a sensitivity of 83 per cent in the initial studies. With further experience sensitivity and specificity rates of about 90 per cent were obtained

The use of the single oblique chest lead electrocardiogram is an effective practical and rapid screening procedure applicable to the study of mass population With this technique 30 to 50 subjects can be screened hourly

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was normal or showed focal hypertrophy related to the ventricular septal defect or the abnormal trabeculae. The aortic orifice had a tendency to be smaller than normal A bicuspid aortic valve was present in 4 of the 6 cases often accompanied by increased hemodynamic change. A widely patent ductus arteriosus was always present. A fetal coarctation was seen in 2 cases. The architecture of the septal and parietal bands was slightly altered. The septal band was in some cases more horizontal than usual and the parietal band was at times somewhat deviated away from the tricuspid valve. The arch of the crista was in some instances narrower than normal

Table I Premature narrowing or closure of foramen ovale Review of literature—Cont d

Author year	*Age*	*Foramen ovale*	*Fossa ovalis*	*Left heart chambers*	*Fibroelastosis*	*Other findings**
Nagel, 1958	20 min.	Closed	Absent	Inconspicuous left ventricle	?	Left atrium distended with blood mitral stenosis with small cusps
Currarino et al.[14] (Case 1), 1959	3 day	Closed	Present	Small	Left atrium and left ventricle	Mitral and aortic stenosis
Currarino et al.[14] (Case 2), 1959	3 days	Closed	Present aneurysm of fossa ovalis	Small	Left ventricle	Mitral and aortic stenosis
B With ventricular septal defect without mitral atresia						
Vernon,[17] 1856	4½ hr	Closed	Absent	Small	?	Absent ductus arteriosus overriding aorta abnormal tricuspid valve with regurgitation
Brody 1953	36 hr	Narrow	Present	Small	Left atrium and left ventricle	Common trunk
Edwards,[11] 1960	10 hr	Closed	?	?	?	Coarctation of aorta
C. With mitral atresia						
M I tosh[19] 1926	5 wk.	Closed	Present	Minute left atrium absent left ventricle	None	Accessory vein from left atrium to superior vena cava aortic stenosis pulmonary congestion
Hyman[20] 1946	31½ hr	Closed	Absent	Small left atrium absent left ventricle	None	No mention of levoatriocardinal vein pulmonary venous blood considered to be returned by bronchopulmonary venous anastomosis ortic atresia pulmonary congestion
Edwards and DuShane[21] 1950	27 day	Closed	Present	Small	Left atrium and left ventricle	Several muscular ventricular septal defects accessory vein from left atrium to innominate vein aortic stenosis probe-patent ductus arteriosus

Table II Premature closure or narrowing of foramen ovale Gross changes

Case number	Age	Sex	Narrowing or closure of foramen ovale	Configuration of atrial septum	Other cardiac malformations not mentioned in text
A. Without ventricular septal defect or mitral atresia					
313	4 h	F	Closure	Right side Left venous valve represented by ridge which makes up proximal portion of limbus. Fossa ovalis small. Small aneurysm in fossa. Left side limbus-like configuration with fossa	Left subclavian artery given off at point of entry of ductus
1017	3 days	F	Closure	Limbus normal. Aneurysm of fossa ovalis. Common Eustachian and Thebesian valve	Entry of right upper pulmonary vein into right atrium
1047	1 day	M	Narrowing	No distinct limbus. Left venous valve represented by ridge. Small spatio interseptovalvulare. Absent Eustachian valve	Enlarged, thickened, spongy left atrial appendage
1005	2 h	M	Closure	Right side Small defective limbus, which is probably left venous valve. Aneurysm of fossa ovalis. Left side Limbus-like region with fossa-like depression	

Table II is continued on page 643

ANATOMY OF THE FOSSA OVALIS REGION IN BOTH GROUPS. There were in general two types of configuration. In one type the fossa was large normal or small in size but normal in architecture with the foramen ovale closed (Figs. 3 and 4). In a second type there was no limbus fossae ovalis clearly seen on the right side, or a defective type of limbus representing the left venous (sinus venosus) valve component of the septum secundum was present (Fig 1) whereas the left side showed a pseudolimbus type of formation (Fig. 2). An aneurysm of the fossa ovalis was frequent (Fig 4)

Clinical-pathologic correlation of Case 31

Clinical history M. G., 2-day-old white female infant, was transferred to Presbyterian-St. Luke's Hospital from another hospital because of progressive cyanosis and dyspnea since birth. She was the product of a 9-month gestation, and her birth weight was 7 pounds 13 ounces. The mother was exposed to German measles during the first trimester of pregnancy. Physical examination revealed a markedly dyspneic and cyanotic infant with a respiratory rate of 70 per minute, pulse rate of 160 per minute, and blood pressure (by flush method) of 40 mm. Hg in the arms and legs. The cyanosis was diffuse. Both radial and femoral pulses were palpable but weak. The lungs were clear to percussion and auscultation. Examination of the heart revealed marked cardiomegaly with the apical dullness extending to the left anterior axillary line at the fifth left intercostal space. There was no precordial bulge or thrill. The first sound was normal. The second sound was accentuated and single and was best heard at the second and third left intercostal spaces. There was a Grade 3, soft systolic murmur over the third and fourth left intercostal spaces. The liver was soft and its edge was palpable 3½ fingerbreadths below the right costal margin. There was no facial or peripheral edema.

Routine blood count revealed a hemoglobin of 13.7 Gm. per cent, red blood cell count of 4.51 million per cubic millimeter, white blood cell count of 14,100 per cubic millimeter, polymorphonuclears 56 per cent, bands 24 per cent, lymphocytes 17 per cent, and monocytes 3 per cent. Routine urinalysis showed 3-plus proteinuria. Chest roentgeno-

grams in the posteroanterior and in the lateral views showed clear lung fields, unusual configuration of the heart, and marked increase in its transverse diameter. In the posteroanterior view the right cardiac border was unusually prominent and the apex was lifted. In the lateral view the anterior cardiac shadow encroached into the chest wall, whereas the posterior border was well separated from the spine. The pulmonary vascular markings were considered by us to be either within normal limits or somewhat decreased. These x-ray films were interpreted as indicating marked right atrial and right ventricular enlargement. A 15-lead electrocardiogram (Fig. 5) showed sinus rhythm, rate of 160 per minute, frontal QRS axis of +160 degrees, tall and peaked P waves in Leads II and V_F and tall qR complexes with symmetrical, inverted T waves in the right precordial tracings. The electrocardiogram was interpreted as indicating severe right atrial and right ventricular hypertrophy compatible with a right ventricular pressure that was at least as high as that in the left.

The clinical diagnoses entertained were (1) mitral atresia (2) premature closure of the foramen ovale or (3) severe pulmonary stenosis or atresia. The infant was placed in oxygen, with no appreciable improvement of her dyspnea and cyanosis. She was digitalized 3 hours after admission to the hospital. The next day she appeared to be less dyspneic and the size of the liver was somewhat smaller. However in the evening she suddenly became more cyanotic and died.

Postmortem examination. Aside from the findings in the heart the pathologic diagnoses were (1) passive hyperemia of the liver and spleen (2) focal hemorrhages in the brain, thymus, and lungs

Table II Premature closure or narrowing of foramen ovale Gross changes—Cont'd

Case number	*Age*	*Sex*	*Narrowing or closure of foramen ovale*	*Configuration of atrial septum*	*Other cardiac malformations not mentioned in text*
B. With ventricular septal defect without mitral atresia					
31	3 day	F	Closure	Limbus normal. Aneurysm of fossa ovalis. Common Eustachian and Thebesian valv	Two ventricular septal defects. Two large muscle bands on posterior septum bridge cavity to inferior wall
413	1 hr (premature)	F	Narrowing	Limbus well formed. Minute openings in septum primum. Aneurysm of fossa ovalis	Abnormal architecture of left side of ventricular septum
491	Stillborn	F	Closure	Limbus well formed. Aneurysm of fossa ovalis. Rete chiari	Abnormal architecture of left side of ventricular septum. Deviated parietal band, with accessory parietal band related to tricuspid val
557	3 days	F	Closure	Left venous valve represented by sharp ridge extending from mouth of superior to inferior vena cava. Limbus thus formed by 2 separate ridges with slit in between. Aneurysm of fossa ovalis	Two ventricular septal defects. Fetal coarctation. Abnormal architecture of left side of ventricular septum. Deviated parietal band with accessory parietal band related to tricuspid valv
833	3 day	F	Narrowing	Left valve represented by powerful ridge which forms incomplete limbus. Aneurysm of fossa ovalis with small opening. Common Eustachian and Thebesian valve	Abnormal architecture of left side of septum
1143	2 days	F	Closure	Left valve represented by ridge at mouth of superior vena cava. Limbus describes small arc. Double combined Eustachian and Thebesian valve which sandwiches in the coronary sinus. Aneurysm of fossa ovalis	Narrow arch for crista. Abnormal orientation of fibers in parietal band. Abnormal architecture of left side of ventricular septum. Right subclavian from distal part of transverse aorta. High origin of left coronary ostium. Fetal coarctation. Wall of ductus resembles aorta



Fig. 1. Premature closure of the foramen ovale th mitral stenosis and aortic tresia. Right atrial and right entricular iew. *SVC* Superior ena. *L* Attempt t limbus formation.

(3 dilatation of the scular channels of the lungs
(4 early bronchopneumonia (bilateral).

Cardiac pathologic diagnoses. Premature closure of the foramen ovale with double entricular septal defect (1) Hypertrophy and dilatation of the right atrium (2 probable hypertrophy and dilatation of the right entricle (3 trophy of the left atrium (4) abnormal formation of the posterior group of papillary muscles of the left ventricle (5) overriding aorta (6) bicuspid aortic valv (7) hemodynamic changes in the tricuspid nd pulmonary lves

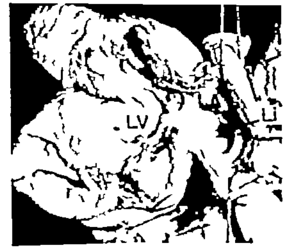


Fig. 2. Same as Fig. 1. Left atrial nd left entricular iew. *L1* Left trium. *Li* Pseudolimbus formation. *LV* Left entricle.

Discussion

A review of our cases and those in the literature reveals that premature closure or narrowing of the foramen ovale may be associated with various complexes. Those with ventricular septal defect but without mitral atresia, and those without ventricular septal defect or mitral atresia but with mitral stenosis and aortic atresia are described above. Our cases fall into these groups. The literature seems to give evidence of a type without ventricular septal defect and without mitral stenosis and aortic atresia. Another complex is that of Edwards,[11] with mitral atresia and levoatriocardinal vein. It is possible that still another complex exists with mitral atresia and without levoatriocardinal vein as in the case of Hyman.[9]

Concerning the architecture of the fossa ovalis region it would appear that the pathogenesis of premature closure varies. It may be related to a lack of formation of an opening in the septum primum to constitute the ostium secundum or an abnormal formation of the septum secundum.

From the physiologic standpoint the premature narrowing or closure of the foramen ovale implies that inferior vena caval blood cannot be shunted to the left atrium as it normally is in fetal life. We are dealing therefore with volume hypertrophy of the right atrium and right ventricle.[22] As discussed elsewhere[22] volume hypertrophy presents itself at autopsy as enlargement of the chamber with a wall which is somewhat thicker than normal or normal. It is thicker than normal because of Laplace's law. We do not know why it is normal in thickness in some cases unless it is because of dilatation due to failure or postmortem dilatation. There is a corresponding volume atrophy of the left atrium and ventricle. However the latter are different in the two types of complexes described in our series. With mitral stenosis and aortic atresia without ventricular septal defect the left atrium is small but thick because of the mitral stenosis. The left ventricle is very small because of the absence of a ventricular septal defect. The cause of its thickness and the fibroelastosis is unknown. They may be due to the aortic atresia and mitral stenosis and retrograde propulsion of blood as has been seen in



Fig. 3. Premature closure of the foramen ovale with ventricular septal defect complex. Right atrial and right ventricular view. *L*, Limbus. *SVC*, Superior vena cava.



Fig. 4. Same as Fig. 3. Left atrial and left ventricular view. *D*, Ventricular septal defect. *A*, Aneurysm of fossa ovalis.

tricuspid stenosis with pulmonary atresia complex. The fibroelastosis may be explained on the basis of stasis and tension. In the complex with ventricular septal defect there is a right-to-left shunt at the ventricular level in fetal life; hence the left ventricle is not so small as in the other type of complex and the lack of aortic atresia or mitral stenosis makes its thickness [illegible] function of the decreased volume according to Laplace's law. It is possible to speculate that the aortic atresia and mitral stenosis in the first type of complex are hemodynamically preordained because of [illegible] tion of flow on the left side due to the closure of the foramen ovale and the absence of a ventricular septal defect. The only blood getting into the left side is that delivered from the pulmonary circuit. In all types of premature closure the ductus is increased in diameter during fetal life. In the type with aortic atresia it supplies the entire circulation.

At birth with the presumed fall in pulmonary resistance there is an increase in pulmonary and left atrial and left ventricular flow. The left side cannot accommodate this flow, which leads to pulmonary vascular engorgement, increased right-to-left shunt through the ductus, right ventricular failure, and death. This course of events is most lethal without ventricular septal defect and least aggravating with levoatriocardinal vein. Thus, death occurs in the first few days of life in most patients with these complexes, but survival may occur up to some months with a levoatriocardinal vein.

The hemodynamic events explain the clinical picture which is characterized by rapidly increasing cyanosis, respiratory difficulty, and congestive heart failure. A review of the clinical data in the reported cases reveal that cyanosis and marked

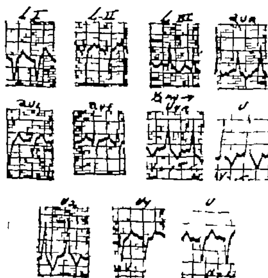


Fig. 5. Electrocardiogram of Case 31 indicating severe right ventricular hypertrophy. Note tall R waves and negative T waves in the right precordial leads, and S complexes with upright T waves in Leads I and V[6] demonstrating discordant T waves.

dyspnea were constant findings and peripheral edema was noted in less than half the cases. In 3 instances[3] the circulatory abnormality resulted in stillbirth with anasarca and hydramnios. The nonspecific systolic murmur in our case and some of the reported cases is probably due to the shunting of blood through the ductus.

Roentgenologic and electrocardiographic information on this anomaly is lacking since most of the patients died shortly after birth. In 4 patients on whom roentgenologic studies were performed the heart appeared to be enlarged in 3[9, 13] and normal in 1.[8] The pulmonary vascular markings were increased in 2[16] and diminished in 1.[1] In our patient marked right atrial and right ventricular enlargement were present and the pulmonary vascular markings were either within normal limits or slightly decreased.

The electrocardiogram in our case and in 2 others showed marked right ventricular hypertrophy. This was associated in our case with a change in the ratio of the weight of the parietal wall of the right ventricle to that of the left ventricle from the normal maximum of 2:1 to 5:1. In Case 1 of Currarino and associates[16] there was left ventricular hypertrophy. At autopsy the left ventricle was small and thick walled with fibroelastosis as in our Group 1.

The similarity between hypoplasia of the aortic tract complex with mitral stenosis and aortic atresia and premature narrowing or closure of the foramen ovale with mitral stenosis and aortic atresia is very marked. It suggests the possibility that hypoplasia of the aortic tract complex is due to a lack of blood flowing into the left side of the heart in fetal life.

The question arises as to what is the criterion for the diagnosis of premature narrowing of the foramen ovale at autopsy. It is self-evident that since the foramen ovale may be of varying size normally and may begin to narrow in the first month of life it is dangerous to make a diagnosis of premature narrowing after the first few days of life. In our opinion in the first few days of life the diagnosis can be made safely only if the foramen measures 0.2 cm. or less in greatest diameter.

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Autoregulation in encapsulated, passive, soft walled vessels

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In some vascular systems a change in perfusion pressure results in an equivalent change in the rate of blood flow in other organs flow follows the change in pressure only momentarily and then the rate of perfusion quickly returns to the original level (autoregulation) This constant blood flow through the tissues whatever may be the height of the general blood pressure defined 60 years ago by Bayliss [1] has been demonstrated in the brain [2] kidney forearm extremities,[3-] heart [11] liver [12] and intestines.[13]

To explain this paradoxical adaptation of vascular resistance Haddy [9] Waugh [1] Folkow and their co-workers, hold that an elevation of arterial pressure stretches the smooth muscle of the vessel wall and thereby stimulates an active vasomotor constriction Since a change in perfusion pressure is accompanied by a transitory change in the rate of flow followed by a rapid return to approximately the earlier rate of flow Stainsby and Renken[14] and Rosenfeld and Sellers [6] consider the autoregulatory response to be evidence for a role of local metabolites.

Langston and associates [15] hold that autoregulation occurs in the kidney only after lymphatic obstruction that follows trauma surgical intervention or ischemia However Haddy and associates[16] have demonstrated that trauma is not a prerequisite.

Hinshaw and associates[8] suggest that renal autoregulation results from a rise in tissue pressure as arterial pressure is raised with proportionate increases in vascular resistance. However the data of Winton [19,21] Gottschalk [22] Swann and associates [23] Miles and deWardener [7] deLangen [24] and Kologlu [25] showing that interstitial pressure changes only slightly even though the arterial pressure is varied over a wide range have been cited [3] to challenge this point of view

Some other properties of autoregulation would appear to complicate the analysis. Thus autoregulation is not evident at low perfusion pressures it is absent in poisoned or traumatized isolated organs. [6 18]

Previous publications from this laboratory demonstrated constant flow over a wide range of perfusion pressures in soft walled tubes[17,23] and in the isolated lung[19] when the venous outlet is lower than the extravascular pressure a rise in the venous pressure in such systems may have

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no effect on the rate of flow despite a concordant reduction of the pressure gradient and a calculated fall in vascular resistance.

In the present study autoregulation is demonstrated in enclosed passive soft walled tubes in which the arterial stream communicates with the extravascular fluid compartment. Although the conclusions drawn *must* necessarily be restricted to the behavior of inert soft walled tubing in the particular arrangement we have used the results may provide some insights into autoregulatory mechanisms.

Method

The apparatus is shown in Fig 1 An aortic reservoir at a selected height P_{A*} produced flow (*shaded*) through the system to a venous outfall at the right. Flow was measured by rotameter timed collection in a graduated cylinder or with an electromagnetic flowmeter A tunnel clamp placed on the rubber arterial segment functioned as an arteriole. The pressure upstream to this tunnel clamp was designated as the arterial pressure P and the pressure immediately beyond it was the arteriolar pressure P_a. The "capillary" was considered to begin at the side arm leading to the inlet and to end at the side arm beyond the escape The capillary flow proper passed through a segment of soft walled latex (Penrose) tubing shown with in-curved walls to enter the venous collecting system at the right. The capillary was enclosed in an extravascular space shown as the darkened circular area with an inlet and outlet connecting with the main stream. Results were similar when the capsule consisted of glass or plastic or of a rubber balloon air accumulating in the capsule also had no effect on equilibrium states. The extravascular pressure P_E was determined by the settings of the "permeability" screw clamps on the side arms leading to the inlet to the extravascular space, and the escape from the extravascular space. In the present report the total flow through the capillary system is given. The capillary consisted of a segment of latex rubber of 0 6 cm diameter and 8 cm. length.

The system could be controlled at four points by varying the height of the aortic pressure head or by tightening or opening the clamps at the arteriole the inlet to the extravascular compartment or the escape from it.

Results

1 Zero extravascular pressure When the inlet clamp was closed and the escape from

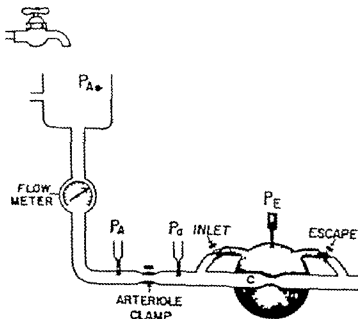


Fig. 1 The apparatus which is described in the text.

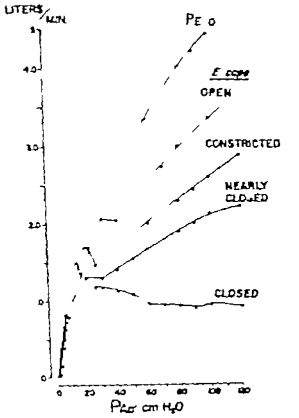


Fig 2 Flow is given in the vertical scale, in liters per minute the height of the "aortic" reservoir (P_{AO}) is given in the horizontal scale, in cm. H_2O The escape from the extra vascular compartment at the venous end of the capillary was fully opened. The connection between the main stream and the extra vascular compartment was occluded with a pinch clamp, permitting the extravascular pressure (P t fall to zero flow under these circumstances is given in the upper line ($P = 0$). Removal of the pinch clamp from the connection between the main stream and the capsule resulted in an increase in extravascular pressure, and flow was reduced (see line labeled *Escape open*) Progressive closure of the escape clamp resulted in flow patterns indicated by the lines labeled *Constricted* and *Nearly closed* When the escape clamp was then completely *Closed*, flow rates remained fairly constant over wide range of aortic pressure head. Discussed in text.

the capsule was open to atmosphere the extravascular pressure was zero ($P_E = 0$) (Fig 2) and flow was a function of the arterial perfusion pressure head.

2 Positive extravascular pressure. When the inlet clamp was opened the main stream communicated with the extravascular space, producing a positive extravascular pressure. The screw clamp on the tube which permitted extravascular fluid to escape to the main stream was then opened to various degrees, and the effect on flow through the vessel was determined. In all of the studies with this model flow increased as a function of aortic pressure head until a critical delivery was achieved. This value varied with the relative facility of inflow into the capsule and escape from it. In the data given below flow rates higher than the critical value sometimes generated an oscillation of the capillary walls, with repetitive partial or complete closure and opening (flutter) at rates ranging from 0 25 to about 40 per second. The rate of oscillation had only a small effect on the rate of flow

A. ESCAPE OPEN As the clamp on the escape tube was opened fully the extravascular pressure fell but remained higher than that of the venous outlet. Flow for a given pressure head was less than that observed when extravascular pressure was at atmospheric levels (Fig 2, *Escape open*) A break in the curve is seen at 2 0 L. per minute beyond which the slope of the flow pressure curve is reduced.

B. ESCAPE CONSTRICTED Tightening of the clamp on the outlet of the capsule was associated with an elevation of extravascular pressure and a reduced flow for a given pressure head (Fig 2) A break in the line was observed at flow rates of approximately 1 7 L. per minute after which a lower slope was observed.

C. ESCAPE NEARLY CLOSED. Further constriction of the escape tube of the capsule resulted in a further rise in extravascular pressure, flow for a given pressure head was further reduced and the break on the tracing occurred at lower flows (Fig 2) In some experiments the escape tube was opened slightly so that the pressure immediately upstream to the soft walled vessel equaled that in the capsule in these studies, flow remained unchanged over a wide range of perfusion pressures.

D. ESCAPE CLOSED. Data given in the line marked *Closed* in Fig. 2 show that flow increased with rising perfusion pressure to a point about 15 cm H_2O at which a flow of 1.5 L. per minute was measured Further increases in perfusion pressure resulted in a fall in the rate of flow flow leveled off at about 1.2 L. per minute and then declined slowly as perfusion pressures were raised above 25 cm. H_2O

Use of a low-sodium formula as an improved Karell diet, with emphasis upon the outpatient management of heart failure and lymphedema

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The dietetic management of patients who have congestive heart failure and other edematous states continues to pose a problem for the clinician. This is true whether he employs a diet which consists solely of regular milk or a salt-poor milk preparation, the rice diet, or a standard low-sodium diet. In addition to such factors as palatability and acceptability—especially when anorexia and other *symptoms attributable to congestive* changes in the abdominal viscera are present—there is the matter of nutritional depletion becoming aggravated by the low protein content of most of these regimens. For example, the standard Karell diet supplies about 26 Gm. of protein daily, whereas the rice diet furnishes from 15 to 30 Gm. of protein daily. These alterations in nutrition can contribute significantly to the asthenia characteristic of the postdiuretic state.

I have employed a food mixture (Metrecal) to great advantage as a modified Karell type of diet in 21 patients with frank congestive heart failure or noncardiac peripheral edema *(Table I). Such usage pr*imarily is predicated upon the presence of only 900 mg. of sodium per quart. Other attributes of this preparation—hereafter also referred to as "formula"—that influenced the adoption of this diet included the presence of 70 Gm. of protein, 20 Gm. of fat (two thirds being unsaturated fatty acids), 3.5 Gm. of potassium, 250 mg. of magnesium, and significant amounts of essential vitamins (i.e., meeting the recommended allowances for normal adults as established by the National Research Council) and other minerals in the same amount of the preparation. Furthermore, it was possible by this means to begin an *intensive program of long-term weight* reduction in those patients who also were moderately or markedly obese at the time of their heart failure—a psychologically opportune occasion for instituting such a program.

Methods

In most instances, one full glass of Metrecal liquid (containing 225 calories and 225 mg. of sodium) was given four times daily. Flavoring was optional. The prepared liquid preparation, either in cans containing individual servings or the quart size, proved to be the most practical. In some patients, the addition or substi*tution of Metrecal pudding (8 ounces con*taining 225 calories) or wafers (each containing 5 calories) proved to be highly satisfactory and tended to minimize monotony. (Each of these forms also contain 1 mg. of sodium per calorie. The newer

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[illegible] supplied by Mead Johnson & Company, [illegible], Ind.

3 Arteriolar resistance The arteriolar screw clamp on the tubing leading to the soft walled vessel (Fig 1) was tightened to simulate the effect of arteriolar constriction In this series of experiments the inlet into the extravascular compartment was open widely while the escape tube was closed

Setting of the aortic perfusion pressure head P_A is indicated by the numbers adjacent to each of the lines. Fig 3 shows flow and extravascular pressures (P_E) recorded at perfusion pressures (P) ranging from 20 to 100 cm. H_2O As the arteriolar screw clamp was tightened intravascular and extravascular pressures at the level of the soft walled segment fell. Thus when P_A was 100 cm. H_2O P_E was 95 as the arteriolar clamp was constricted P_E fell progressively (*horizontal scale*) Flow decreased somewhat at first and then increased until P_E was approximately 10 cm. H_2O and flow was about 1 L. per minute. As the arteriolar clamp was constricted further flow fell sharply toward zero

Fig 3 shows that in the ranges tested the flow rate was essentially independent of either the perfusing pressure head or the intravascular or extravascular pressures.

4 Adaptation The outlet of the extravascular chamber was clamped The screw clamp on the inlet to the extravascular chamber was tightened to decrease the rate of equilibration of intravascular and extravascular pressures. To determine instantaneous flow a rotameter or the probe of an electromagnetic flowmeter* was inserted into the system between the reservoir and the soft walled tube.

Changes in perfusion pressure head produced immediate and concordant changes in flow followed almost at once by a grad

*The electromagnetic flowmeter studies were facilitated through the kindness of Dr Wm. Chardack of the Buffalo Veterans Administration Hospital.

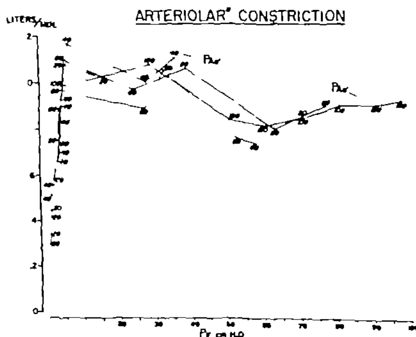


Fig 3 Relation of extravascular pressure to flow rate. Flow in liters per minute is given in the vertical scale Extravascular pressure (P), in cm.H_2O, is given in the horizontal scale. The escape from the extravascular chamber was closed. Tests were made with the aortic reservoir 100, 80, 60, 40, and 20 cm.H_2O above the level of the soft-walled vessel the numbers adjacent to the points on each line identify the aortic pressure head. Tightening of the arteriolar clamp lowered the extravascular pressure as indicated for given P_A. Flow was affected to only small extent and even increased just prior to the point at which the arteriole was almost completely obstructed.

ual return to approximately control values (Fig 4) This adaptation process could be accelerated by opening the screw clamp on the inlet to the extravascular space it could be slowed by introducing a compliance such as a water manometer into the extravascular compartment

A drop in perfusion head (*A* *C* *D* Fig 4) resulted in an immediate fall in intravascular pressure since the extravascular pressure fell more slowly the resulting negative transmural (intravascular < extravascular) pressure compressed the soft walled vessel and flow fell sharply As transmural pressure returned toward zero compression of the soft walled vessel was gradually eased and flow returned to approximately control values.

A rise in perfusion pressure (*B* *E* Fig 4) produced a positive transmural pressure which distended the soft walled vessel and flow increased as extravascular pressure gradually increased to the new level flow returned to approximately control values.

Autoregulation was also observed when the arteriolar clamp was tightened (*F* Fig 4) the pressure beyond the arteriole fell sharply and flow fell from 0 7 L. per minute to as low as 0.5 L. per minute but then returned to 0 6 L. per minute At *H* (Fig 4 the arteriolar clamp was re-[illegible]ed intravascular pressure returned to 1 5 cm H_2O and flow increased markedly to 2 3 L. per minute flow then returned in about 15 seconds to 0 75 L. per minute

Discussion

The foregoing results suggest that autoregulation may be a special case of flow through an enclosed passive soft walled vessel When the extravascular space is in communication with the main stream flow for a given perfusion pressure is less than that observed when extravascular pressure is at atmospheric levels. The connection of the main stream with the extravascular compartment may be considered to simulate the passage of fluid through the arteriolar end of the capillaries into the extravascular spaces of encapsulated tissues with a consequent rise in the tissue pressure

Restriction of outflow from the capsule results in a rise in extravascular pressure and a decrease in flow for a given perfusion pressure When the outlet of the capsule is nearly or completely closed flow remains fairly constant despite wide variations in perfusion pressure (autoregulation) (Fig 2)

The results suggest that delivery is modified by the operation of hydrodynamic factors which modify transmural pressure. When both the outlet from the soft walled vessel and the escape from the capsule are closed flow ceases and the pressure inside and that outside the soft walled vessel are equal i.e transmural pressure is zero When the outlet of the soft walled vessel is opened the pressure inside the vessel falls as flow begins in accord with the law of conservation of energy As transmural pressure becomes negative (extravascular pressure exceeds intravascular pressure) the lumen becomes narrowed and delivery is less than that observed when transmural pressure is zero Flow through the extravascular space also tends to lower extravascular pressure but this effect is probably small Ultimately an equilibrium is achieved in which the vessel remains partially collapsed or in recurrent oscillation

The autoregulatory behavior of the soft walled Penrose vessel bears certain similarities to the phenomenon of autoregulation reported to occur in various tissues. Thus at low perfusion pressures delivery varies with pressure and autoregulatory behavior is absent Autoregulation becomes evident at higher perfusion pressure values this relative constancy of flow is not necessarily associated with changes in extravascular pressure. Furthermore a period of time is required for adaptation of flow after a change in the perfusion pressure

The possibility that autoregulation of flow through a segment of Penrose tubing is similar to that of flow through the tissues deserves discussion Since the stiffness of the wall of the capillary is minimal this collapsible vessel appears to be particularly suited to play an important role in autoregulation When the extravascular space surrounding a collapsible vessel such as a capillary in an encapsulated interstitial space is in communication with the stream as by means of a semipermeable membrane the transmural pressure gra

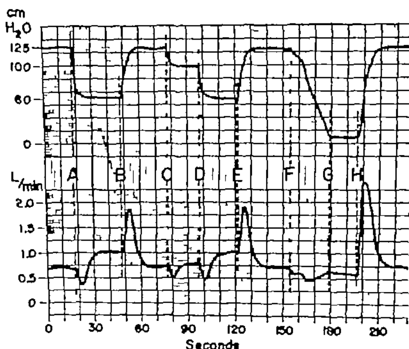


Fig 4 Adaptation. The model is as in Fig 1 the escape clamp was closed. The *figure is simultaneous recording of pressure beyond the arteriolar screw clamp* (*upper line*) and an electromagnetic flow recording (*lower line*). The horizontal scale represents time, as noted For tests 4 through *F* the arteriolar clamp was opened widely Abrupt changes in the height of the perfusion reservoir are accompanied by immediate and concordant changes in flow but within few seconds the rate of flow begins to revert to approximately the control level. At *F* and beyond, the aortic reservoir is held at 125 cm.H_2O as the arteriolar clamp is tightened, the pressure beyond this point of constriction falls, but flow is affected only minimally and tendency to return to control flows can be seen. At *H* the arteriolar clamp is removed flow and pressures (intravascular and extravascular) rise sharply but flow then autoregulates to approximately control values at 220 seconds.

dient can be expected to diminish and the vessel wall will be unstressed relatively small forces can then greatly modify the lumen. In such a system an increase in perfusion pressure is associated with an immediate increase in flow through the lumen however the increased velocity of the stream through the vessel will tend to lower the intravascular pressure As more fluid moves into the extravascular compartment the pressure in this space will rise and the transmural pressure will return to its near zero value. The increased rate of perfusion of the extravascular compartment may also contribute to a slight lowering of the extravascular pressure. These effects may summate in a state of equilibrium in which the rate of flow through the unstressed vessel returns to essentially control values, as in the model experiments. Similarly the sequence of events after a reduction in perfusion head may include an immediate fall in intraluminal velocity a new equilibrium of intravascular and extravascular pressures and flows widening of the vessel lumen and return to approximately control flow rates.

The extravascular pressure is intermediate between the pressures at the arteriolar and venous ends of the soft walled vessel. When the upstream connection is in communication with the extravascular compartment the extravascular pressure rises in the direction of the perfusion head. The facility of return of extra

vascular fluid to the main stream reflects the permeability of the intervening communication in the model this is controlled by the escape clamp. It was of interest that the extravascular pressure and through this the rate of flow could be controlled quite satisfactorily by regulation of the resistance to outflow from the extravascular compartment Thus when the escape from the chamber was completely obstructed a rising perfusion pressure actually resulted in a slight fall in delivery (Fig 2 *Escape closed*) Provision for a slight escape from the chamber resulted in a more constant rate of delivery independent of the perfusion pressure

A significant factor in the control of the rate of vascular flow may thus depend on the control of extravascular pressure Thus, as permeability of the upstream segment of a soft walled vessel in a capsule increases extravascular pressure tends to approach the upstream pressure and flow is reduced accordingly On the other hand an increase in permeability of the venular end of such a vessel lowers the extravascular pressure in the direction of the venous pressure and flow increases as the vessel becomes relatively distended The increased flow through the extravascular compartment in the case of the capillary is thus associated with an increased delivery of nutrients to the surrounding cells and a more rapid disposal of cellular waste products.

Adaptation of flow through perfused organs has been attributed to the time required for changes in the accumulation or washout of metabolites which affect the arteriolar muscle tone [11] The model experiments also show a period of adaptation in which flow varies with the change in perfusion pressure before returning to approximately the control levels provided that the extravascular compartment is in communication with the upstream end of the soft walled tube The period of adaptation in tissues may also reflect only the time required for the passive return of the transmural pressure to approximately zero values

The negligible changes in extravascular pressure observed in tissues as arterial pressure is varied may be accounted for on the basis of the large drop in pressure at the arterioles (Fig 3) Thus a high arteriolar resistance may have an important effect on extravascular pressure even though flow is unaffected unless the arteriole is nearly completely closed This finding suggests the possibility that the arteriole may function more as an on-off valve than as the primary regulator of flow commonly attributed to it.

Loss of autoregulation may result from loss of any of the mechanical factors required for this phenomenon an encapsulated permeable soft walled unstressed vessel In tissues injury to the capsule will eliminate the balance between intravascular and extravascular pressures and flow will tend to vary with perfusing pressure. Poisons can be expected to modify the permeability of the membrane of the critical soft walled vessels and to produce changes in transmural pressure.

The recurrent oscillation of the Penrose tubing raises questions concerning a similar motion of the collapsible vessels which contributes to autoregulation. It is known that capillaries do show recurrent closure and opening [11] Some of these oscillations may reflect interchanges between positive and negative transmural pressures as a result of flow rather than being a response to vasoactivity The rapid oscillation observed in the present studies appears to be diminished in frequency when several Penrose vessels are enclosed in the same capsule as noted in studies being prepared for publication

Since autoregulation can be demonstrated in purely mechanical arrangements of inert permeable enclosed vessels it is suggested that similar structural relationships may account for autoregulatory phenomena in various tissues.

Summary

Flow through an enclosed passive soft walled vessel remained at fairly constant values (autoregulation) despite marked changes in perfusion pressure The system consisted of an aortic reservoir connected to a segment of Penrose tubing which was enclosed in a glass capsule the capsule was connected to the upstream segment of the soft walled vessel to permit a "transudate" to enter the extravascular space Controlled escape of fluid from the capsule permitted

regulation of the extravascular pressure. A tunnel clamp on the arterial inlet served as an arteriole flow remained relatively unchanged when this arteriolar screw clamp was tightened almost to the point of obstruction of flow. The system displayed other properties of autoregulating tissues, such as absence of autoregulation at very low perfusion pressures and a lag in the adaptation of resistance to change in pressure. These effects result from an interplay of the transmural pressure and the pressure/flow relationships within and without the soft walled vessel as discussed. The results suggest that autoregulation may be a mechanical property of the effect of flow on the wall of enclosed collapsible vessels. A limited role for the arteriole in such a system is indicated.

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The systemic and coronary hemodynamic effects of synthetic bradykinin

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Since the original description of the action of bradykinin[1] and particularly since its isolation[2] and synthesis,[3] there has been considerable interest in its various physiologic effects. There has been recent interest in both local[4] and general[5] hemodynamic effects. The present series of investigations was begun prior to presently available reports of the systemic and coronary hemodynamic effects of this material[5] and report the effects of the infusion of synthetic bradykinin† in intact anesthetized animals.

Material and methods

The study was carried out in fasting mongrel dogs. Anesthesia was induced by 3 mg. per kilogram of morphine injected subcutaneously, followed 1 hour later by a 50/50 mixture of veterinary pentobarbital and Dial urethane‡ given in a dose of 0.25 ml. per kilogram of body weight. Cardiac output was determined by the Fick principle and coronary blood flow by the nitrous-oxide method during the saturation phase, utilizing a blood myocardial partition coefficient of 1.0. Blood gas analyses were done by the method of Van Slyke-Neill, whereas the nitrous-oxide analyses were done by the method of Orcutt and Waters. Expired air was analyzed by the method of Scholander. Blood pH was determined by the Cambridge Model R pH meter. Pressures from the femoral and pulmonary arteries and the right atrium were recorded via Statham strain gauges on the Gilson macropolygraph. Mean pressures were determined by electrical integration. Calculations were made by standard formulas, and comparisons were made utilizing the "t" test for significance. The "t" test for paired data was used in those situations in which each animal served as his own control, and the "t" test for grouped data was used otherwise.

Bradykinin was administered into the

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†Bradykinin (synthetic) was generously supplied by Dr. R. Bircher of the Sandoz Laboratories, Hanover, N. J.

‡Dial-urethane, furnished through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, N. J., contains 100 mg. of Dial, 400 mg. of monoethylurea, and 400 mg. of urethane per milliliter. Veterinary Nembutal contains 60 mg. of pentobarbital per milliliter.

right atrium of animals which varied in weight between 16 and 25 kilograms (average 21 1 kilograms) by continuous infusion with a Harvard Apparatus Company constant injector Rates of administration were 0 2 0.3 1 and 2.5 µg per kilogram per minute Since the response seemed to be more pronounced and more stable at a dose of 2.5 µg per kilogram per minute 8 animals were studied with this dose. After control observations of cardiac output and coronary blood flow there was a 20-minute waiting period before the second study in order to permit the dog to excrete the nitrous oxide which had been absorbed during the first measurement of coronary flow The administration of bradykinin was begun 5 minutes before the second determination of cardiac output and was continued throughout the determination of cardiac output and coronary blood flow Thus approximately 20 minutes of continuous infusion of bradykinin was required

In 5 dogs, cardiac output was determined by the indicator-dilution method alone utilizing indocyanine green dye a cuvette densitometer and the Gilson macropolygraph as a recorder in order to establish the hemodynamic effects during the period when the arterial pressure was reduced immediately after the onset of infusion of bradykinin as well as during the time when the pressure tended to rise again Repeated determinations were made with the infusion alternately turned off and on in order to have repeated control and experimental observations. Two of these 5 dogs were control animals, whereas 3 had been pretreated with reserpine to deplete their catecholamines. In 3 more dogs which were pretreated with reserpine complete hemodynamic studies were made with determination of cardiac output by the Fick principle and coronary flow by the nitrous-oxide method during the infusion of bradykinin into the right atrium at the rate of 2.5 µg per kilogram per minute. In the reserpine-pretreated animals the dose of anesthetic was reduced because such animals are apt to die if anesthetized in the usual manner Therefore anesthesia was secured by slow administration of the Dial urethane-Nembutal mixture intravenously without premedication by morphine and in a dose sufficient to secure anesthesia without excessive depression.

In 7 dogs which varied in weight between 21 and 25 kilograms (average 22.6 kilograms) transseptal left atrial puncture was done[7] and bradykinin was infused into the left atrium. The first animal and the last 4 animals received bradykinin at the rate of 2.5 µg per kilogram per minute. The dose was reduced for the second and third animals because of the marked hypotensive response obtained in the first, and these 2 animals received 0.5 and 1 25 µg per kilogram per minute, respectively The remainder of the animals received 2.5 µg per kilogram per minute because of th reduced cardiac rate in the second and third animals, and because it seemed that the size of the dose was not the cause of the variability of the response on left atrial injection. Furthermore since the size of the dose was not clearly demonstrable as the cause of variability the findings in all of these animals are summarized together as shown in Table II

Results

With the smaller doses of bradykinin there was a consistent increase in cardiac rate accompanied by a decrease in systemic arterial pressure and peripheral vascular resistance. Neither cardiac output nor coronary blood flow was significantly changed thus the larger dose was used in the remainder of the study so that the hemodynamic response would be defined more precisely

Results for the steady state in the 8 control animals which received bradykinin into th right atrium in the dose of 2.5 µg per kilogram per minute are summarized in Table I and graphically revealed by the typical response of one animal in Fig 1 When administration of bradykinin was started there was an immediate increase in the cardiac rate accompanied by a considerable decrease in the system c arterial pressure. The systemic arterial pressure then tended to rise w th a transient over shoot above the level it would finally atta n during the infusion and eventually to equilibrate Thus at the time of the second hemodynamic study the over-all mean arterial pressure was reduced when com

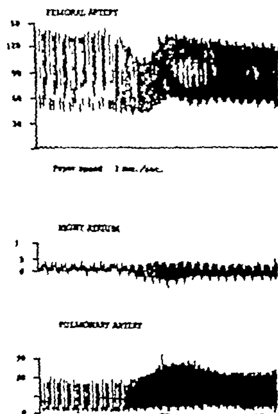


Fig. 1. [illegible] hemodynamic effects of bradykinin. These pressure tracings reveal the typical response [illegible] (1.5 μg/kg/min) of synthetic bradykinin [illegible] the right atrium of a normal dog. At the end of this [illegible] the response has become [illegible] stable.

pared to the onset of observations. The pulmonary arterial pressure tended to rise acutely with an increase in the pulse pressure and then underwent a gradual sustained decrease toward control observations. Although the tachycardia persisted at the time of the determination of cardiac output and coronary flow during infusion of bradykinin, the pulmonary arterial mean pressure had returned to a control level. Right atrial pressure tended to undergo considerably greater systolic and diastolic excursions immediately after the onset of administration of the drug, but there was relatively little change in the mean. Gradually, however, as the infusion continued, right atrial pressure decreased, and at the time of the second hemodynamic determinations was significantly lower than during the control period. The immediate respiratory response to administration of the agent was a moderate increase which tended to return toward the control rate but continued to be significantly greater than the control rate, with a moderate increase in respiratory rate. Body oxygen consumption was increased slightly but significantly. The carbon-dioxide excretion was increased to a greater degree, due in part to the increase in ventilation, and consequently the calculated respiratory quotient was higher. Significant increases occurred in the arterial hemoglobin, hematocrit, and oxygen content, while the arteriovenous oxygen difference narrowed. Although the coronary sinus oxygen content did not change, because of the increase in the arterial oxygen content there was widening of the arterial-coronary sinus oxygen difference. Since there was similar widening of the coronary sinus-arterial carbon dioxide difference, the calculated cardiac respiratory quotient was not significantly altered. Cardiac output was significantly increased, as were right and left ventricular work, whereas both systemic arterial and total pulmonary resistance were reduced. Coronary blood flow was significantly increased, as was the myocardial oxygen consumption, whereas coronary vascular resistance was reduced. The cardiac efficiency index, which relates left ventricular work to left ventricular oxygen consumption, was not significantly changed.

As can be seen in Fig. 2, the results of the studies of hemodynamics by indicator-dilution curves indicated a considerable increase in the cardiac output as soon as it could be determined after the onset of the continuous infusion of bradykinin. Furthermore, with the increase in cardiac rate there was considerable peripheral vasodilatation and a decrease in calculated total peripheral and pulmonary resistance. There were no basic hemodynamic differences between the acute and the sustained administration of bradykinin, except that the effects were more pronounced when measured shortly after the onset of administration of the drug; then gradual readjustment toward the control state took place during more prolonged infusion.

Administration of the agent into the left atrium (Table II) revealed that the systemic hemodynamic effects were simila

Table I. Hemodynamic effects of continuous infusion of bradykinin (2.5 μg/Kg/min) into the right atrium of control dogs

Parameter	Control	Study	SEM diff	% Change	p Value <
Cardiac rate	74	130	6.785	+75.7	0.001
Mean systemic arterial blood pressure (mm. Hg)	108	100	3.818	−7.4	0.1
Mean pulmonary arterial blood pressure (mm. Hg)	13	12	0.567	−7.7	0.2
Mean right atrial blood pressure (mm. Hg)	3.8	2.3	0.370	−39.5	0.01
Oxygen consumption (ml./min.)	100	111	2.151	+11.0	0.01
Body respiratory quotient	0.84	0.93	0.022	+10.7	0.01
Arterial hematocrit (%)	43	46	0.627	+7.0	0.001
Arterial hemoglobin (Gm./100 ml.)	14.3	15.3	0.194	+7.0	0.01
Arterial oxygen content (ml./100 ml. blood)	17.1	19.0	0.373	+11.1	0.01
Arteriovenous oxygen difference (ml./100 ml. blood)	3.8	2.6	0.193	−31.6	0.001
Coronary sinus oxygen content (ml./100 ml. blood)	5.5	5.5	0.357	0.0	—
Cardiac output (L./min.)	2.7	4.3	0.215	+59.3	0.001
Left ventricular work (Kg.M./min.)	4.1	6.0	0.336	+46.3	0.001
Right ventricular work (Kg.M./min.)	0.5	0.8	0.078	+60.0	0.01
Total peripheral resistance (c.g.s. units)	3,240	1,880	139.795	−42.0	0.001
Total pulmonary resistance (c.g.s. units)	386	230	28.627	−40.4	0.001
Coronary blood flow (ml./100 Gm./min.)	83	104	8.228	+25.3	0.05
Coronary vascular resistance (units)	1.38	0.98	0.120	−29.0	0.02
Left ventricular oxygen usage (ml./100 Gm./min.)	9.3	13.6	0.890	+46.2	0.01
Index of efficiency	0.43	0.46	0.036	+7.0	0.6

*SEM diff.: Standard error of the mean difference between control and experimental studies.

Table II. Hemodynamic effects of continuous infusion of bradykinin into the left atrium of control dogs

Parameter	Control	Study	SEM diff	% Change	p Value <
Cardiac rate	87	151	16.968	+73.6	0.01
Mean systemic arterial blood pressure (mm. Hg)	112	85	7.567	−24.1	0.02
Mean pulmonary arterial blood pressure (mm. Hg)	14	13	1.354	−7.1	0.5
Mean right atrial blood pressure (mm. Hg)	2.9	2.0	0.415	−31.0	0.1
Oxygen consumption (ml./min.)	112	108	2.420	−3.6	0.2
Body respiratory quotient	0.80	0.90	0.052	+12.5	0.9
Arterial hematocrit (%)	42	47	0.831	+11.9	0.001
Arterial hemoglobin (Gm./100 ml.)	14.5	16.1	0.237	+11.0	0.001
Arterial oxygen content (ml./100 ml. blood)	16.6	19.6	0.755	+18.1	0.01
Arteriovenous oxygen difference (ml./100 ml. blood)	3.7	3.1	0.264	−16.2	0.1
Coronary sinus oxygen content (ml./100 ml. blood)	6.8	6.1	1.091	−10.3	0.6
Cardiac output (L./min.)	3.1	3.5	0.211	+12.9	0.2
Left ventricular work (Kg.M./min.)	4.8	4.1	0.577	−14.6	0.3
Right ventricular work (Kg.M./min.)	0.6	0.7	0.093	+16.7	0.4
Total peripheral resistance (c.g.s. units)	2,985	1,956	61.997	−34.5	0.001
Total pulmonary resistance (c.g.s. units)	377	300	35.598	−20.4	0.1
Coronary blood flow (ml./100 Gm./min.)	97	104	15.422	+7.2	0.7
Coronary vascular resistance (units)	1.22	0.94	0.117	−23.0	0.1
Left ventricular oxygen usage (ml./100 Gm./min.)	9.4	13.0	1.527	+38.3	0.1
Index of efficiency	0.51	0.34	0.079	−33.3	0.1

*SEM diff.: Standard error of the mean difference between control and experimental studies.

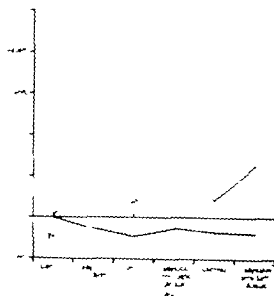


Fig. The ... and pulmonary hemodynamic effects of bradykinin as revealed ... control animal ... indicator-dilution curves. These results are typical of other similar studies. The indicator dilution curves were made very promptly after the onset of infusion of bradykinin and reveal that the hemodynamic response to acute infusion is similar to the response to chronic infusion. The infusion was then discontinued and after the animal had returned to what appeared to be the control state observations were made again. This process was repeated as indicated. Each observation on the graph is the result of averaging figures obtained from observations during two or three indicator-dilution curves. Blood withdrawn during these curves was infused again after each curve; hence the loss of blood is not a factor in these results. *RVW*, Right ventricular work, in kg. meters/min. *LVW*, Left ventricular work in kg. meters/min. *CO*, Cardiac output, liters/min. *PVR*, Total pulmonary resistance in ... *PVR*, Total peripheral vascular resistance ... units.

to those of administration into the right atrium except that the decrease in mean systemic arterial blood pressure was more pronounced and the increase in cardiac output was sufficiently less so that the left ventricular work failed to increase significantly. The total pulmonary resistance decreased less during left atrial injection. In 5 of the cases of infusion of bradykinin into the left atrium coronary flow actually decreased, whereas in 1 there was no change and in 1 there was a considerable increase. It should be noted that the control state was more variable with a higher cardiac rate and a considerable increase in resting coronary flow in these animals possibly associated with the manipulation of transseptal puncture and the production of some unavoidable trauma. In each animal the heart was inspected and those animals with clearly major trauma were eliminated; however, some trauma is inevitable in such procedures.

In the 6 animals pretreated with reserpine, cardiac rate increased (+20.8 per cent, $p < 0.05$) and mean systemic arterial blood pressure decreased (−16.5 per cent, $p < 0.01$) with a decrease in peripheral resistance (−39.3 per cent, $p < 0.01$), an increase in cardiac output (+43.3 per cent, $p < 0.05$) and a variable but insignificant increase in left ventricular work (+24.4 per cent, $p < 0.2$). The control heart rate was considerably more rapid in these reserpinized animals and possibly as the result of this the increase in rate after administration of bradykinin was less ($p < 0.02$) than in the control animals. Furthermore, the hypotensive response tended to be greater in the reserpinized animals and the tendency of control animals to recover rapidly toward normal shortly after administration of the drug was no longer observed (Fig. 3). Although the response in cardiac output was somewhat less, statistical testing revealed no significant differences from the responses in control animals in any of the parameters except cardiac rate. In the 3 reserpinized animals in which complete hemodynamic studies were made subsequent to administration of the agent into the right atrium the data are not quite so clear as they are in the non-pretreated control animals, probably for several reasons. (1) The reserpinized dogs had rather severe diarrhea, were more sedated, and probably less well hydrated than were the control animals. (2) Because of this state of the animals there was variation in the dose of anesthetic, since each animal was given only enough to attain light anesthesia. (3) The response to bradykinin was more variable; this possibly was due to differences in the control state of the animals and in the state of anesthesia. Even though fewer experiments were done, the hemodynamic effects were sufficiently consistent to indicate peripheral vasodilatation with systemic arterial hypotension accompanied

soup product, however, contains substantially more sodium and was not used in these studies.) The diet was supplemented by judicious amounts of water and occasionally by one glass of orange juice. Accordingly, most patients received an average of 1.0 Gm. of sodium and 1,000 calories daily, unless the need for stricter sodium restriction or great obesity warranted the use of lesser amounts.

For patients who had congested livers due to existing or recent heart failure, a full glass of formula at bedtime and another one-half or one glass at 2 A.M. (or whenever the patient would awaken to urinate) was insisted upon to obviate or to minimize nocturnal hepatic hypoglycemia. Although such hypoglycemia may be difficult to document in outpatients, it poses an important potential complication under these circumstances and must be anticipated. (Paradoxically, the possibility of hypoglycemia is only rarely entertained as an explanation for disordered behavior, seizures, episodic coma, palpitation, angina pectoris, ulcer type of pain, and sweating in patients with congestive heart failure whom I have seen in consultation. The nocturnal aggravation of these symptoms poses an important diagnostic clue.) Others have empirically recommended that the diet of a patient who has congestive failure and hepatomegaly be divided into as many as six small feedings.[2] One patient with pulmonary embolism and angina pectoris (Case 9) successfully lost 20 pounds on the formula, but would repeatedly experience hypoglycemic episodes if he did not consume a full glass for lunch. When his clinical course was complicated by congestive heart failure at a later date, the ingestion of the liquid or pudding at bedtime and in the early morning effectively prevented symptomatic hypoglycemia.

In both diabetic and nondiabetic patients, hypoglycemia specifically must be guarded against when coronary heart disease is present, because of the potential aggravating effect of a lowered blood sugar. Nondiabetic patients who gave a history consistent with functional hyperinsulinism several hours after eating were accordingly encouraged to take nourishment at regular intervals between meals. The routine use of several formula wafers (perhaps with artificially sweetened tea or decaffeinated coffee) at approximately 10 A.M. and 3 P.M. and the investigation of several wafers at the first clinical evidence of hypoglycemia has proved eminently helpful in managing this complication in obese cardiac patients. In the case of diabetic patients who required insulin or one of the oral drugs effective in controlling hyperglycemia, specific instructions were given concerning the ingestion of snacks—usually at 3 P.M. and at bedtime. Here again, the wafers and puddings were effectively utilized because of the ease with which they could be subsequently incorporated into the exchange system of foods, i.e., three wafers or a one-third serving of pudding approximate one bread exchange. Excessive consumption of tobacco was curtailed in these individuals in view of its recognized importance in the genesis of postprandial hypoglycemia, as well as its detrimental effect on cardiovascular function. Another reason for the strict avoidance of hypoglycemia in diabetic patients is the conviction shared by myself and others that repeated hypoglycemic stress plays an important role in the genesis and aggravation of diabetic retinopathy[4] and diabetic neuropathy.

The use of formula as either a supplement to or replacement for standard low-sodium meals also has been employed to great advantage in patients who have chronic congestive failure, particularly during periods of anorexia. Under these circumstances, it is frequently accepted by the patient when other nutrients are not. This was so in a number of cardiac patients not included in the present series.

Most of the cardiac patients in this study had been on maintenance digitalis. Digitalis was purposely withheld in 3 individuals (Cases 3, 4, and 7), however, and was thereafter found not to be necessary after they had lost both their edema and fat. In this regard, Gorlin has pointed out that any agent which causes reduction of the blood volume can be of value in managing heart failure, since the cardiac size is reduced thereby and the heart functions more efficiently. This may variously be accomplished by diuretics, phlebotomy, and digitalis—or even by the sole use of bed rest and a low-salt diet.

by coronary vasodilatation adequate to maintain coronary flow. Myocardial oxygen consumption increased in 2 of the 3 experiments.

Discussion

The systemic and coronary hemodynamic effects of bradykinin as administered to control animals, are similar to those that have been reported in studies which utilized the same basic type of preparation but in which a larger dose was given.[8] These conclusions are also compatible with the work indicating that bradykinin is a peripheral vasodilator [] and with the report of isolation of bradykinin from human skin during the course of heat-induced cutaneous vasodilatation.[]

When it was observed that the arterial hemoglobin and hematocrit rose accompanied by an increase in cardiac output, coronary blood flow and myocardial oxygen consumption the question arose whether there was a release of catecholamines. The experiments were done, therefore, in animals reserpinized in the manner which has been recommended to produce depletion of catecholamines. It is of considerable interest that the hemodynamic effects of bradykinin were basically the same after the administration of reserpine. From the facts that the secondary rise in arterial pressure did not occur and the reduction in systemic arterial pressure was more pronounced, it seems likely that catecholamines may be released during the hypotensive response to the administration of bradykinin as a homeostatic mechanism. Such a response might be expected to occur with acutely induced hypotension of almost any origin.

The administration of bradykinin into the left atrium was done in order to test the hypothesis that passage through the pulmonary circulation inactivates bradykinin. In general, no evidence was found to support the hypothesis; however, the control coronary flow in many of those animals which had transeptal puncture was increased above the usual normal, and in the presence of a high resting coronary flow no further increase occurred. This is noted to be true both for the injection of bradykinin into the right and into the left sides when the data of individual dogs are reviewed (Table III). Hence, in those animals with normal or low coronary flow an increase was observed unless there was a marked systemic hypotensive response, whereas in those with a high resting coronary flow a decrease occurred in spite of the fact that the systemic hemodynamic effects were not different. This response in the coronary circulation may probably

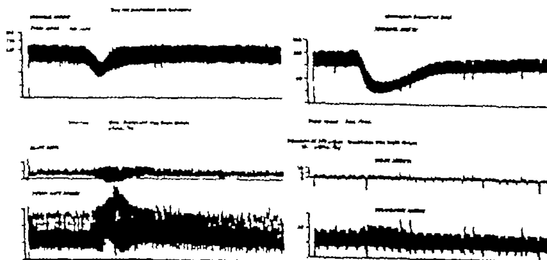


Fig. 3. The systemic hemodynamic response to comparable single dose of synthetic bradykinin in a control (left) and reserpine-pretreated dog (right). The responses in the femoral and pulmonary arterial pressures are notably different. Right atrial pressure of the reserpinized animal is somewhat damped but shows no real change.

Table III Coronary blood flow (ml /100 Gm) before and during infusion of bradykinin at the rate of 2 5 μg Kg min

Right atrial infusion			Left atrial infusion			Right atrial infusion (except ne-pretreated dogs)		
Control		Experimental	Control		Experimental	Control		Experimental
48	→	86	79	→	76	51	→	52†
58	→	109	86	→	183	63	→	100
75	→	82	101	→	95	65	→	113
77	→	108	128	→	103			
89	→	135	140	→	128			
91	→	103						
111	→	108						
111	→	*100*						

*Drop in mean arterial blood pressure of 37 mm. Hg.
†Mean arterial blood pressure fell to 33 mm. Hg.

be considered to be due to differences in the control state of the vessels, as has been suggested for the bidirectional action of serotonin Thus when the vessels of the forelimb were neurogenically constricted net dilatation resulted from the infusion of serotonin whereas during neurogenic vasodilatation net constriction occurred [11] This variability of response also recalls the demonstration that when neurogenic tone is high serotonin produces primarily a hypotensive response whereas when tone is low the response becomes hypertensive.[12] The pattern of dilatation of capillaries, vessels and veins and constriction of arteriovenous anastomoses in the fingers has already been shown to occur during infusion of bradykinin thus, the possibility that a similar reaction occurs in the heart must be considered It is known that bradykinin is inactivated in blood[7,8] and probably in the tissues as well. Since with the right atrial injection more time elapses until the polypeptide reaches the systemic and coronary vessels where its vasodilatory response is probably produced there is more time for the lytic system in the blood to become active before the agent reaches its effector In spite of these considerations, we did not demonstrate any remarkable differences other than those already discussed including the probable decreased dilatation of the pulmonary vessels.

The modest increase in coronary blood flow demonstrated after right atrial injection must be considered in relation to factors known to be related to coronary flow Thus when the increase in flow is compared to the increase in rate, it is seen that the flow per beat actually decreased (−27 per cent $p < 0.05$) as did the flow per unit of oxygen consumed by the left ventricle (−15.4 per cent $p < 0.05$) furthermore, the coronary sinus oxygen content did *not increase. It is doubtful* then that bradykinin can be classified as a very potent coronary vasodilator when systemically administered in *the doses* used in this study Furthermore, in the previous report coronary flow did not increase as much as myocardial oxygen consumption and the coronary sinus oxygen content actually decreased If bradykinin were locally released in areas in which increased blood supply is required as seems probable [13] it could conceivably be of much greater significance.

The basic similarity of the response of *the peripheral and of the coronary* circulations to the administration of bradykinin recalls that which is produced by exercise and has given rise to speculation *whether* this compound is released peripherally during exercise.[13] It is obvious that the similarity of the hemodynamic response *to* bradykinin and to exercise *does* not constitute biologic proof of their relation and further investigation into this area would

appear to be desirable. Attempts to isolate bradykinin from the venous blood of tetanically contracting muscle have been unsuccessful.[13] Although bradykinin-like material was isolated from the perfused tongue the question of its origin from glands within the tongue was not settled.[13] *Since bradykinin is known to produce pain* when infused into peripheral arteries and since the pain is similar to that induced during restoration of circulation after application of a tourniquet the possibility exists that this substance may be released in tissues in response to ischemia and produce pain if its rate of clearance is not adequate. The coronary vasodilating and the algesic properties of this agent raise the possibility that bradykinin is at least one of the substances released in the myocardium in response to ischemia and may be partially responsible for anginal pain. Again further data are required.

Summary

1 The systemic and coronary hemodynamic effects of bradykinin have been studied during its infusion into anesthetized dogs.

2 The administration of bradykinin is associated with decreased peripheral pulmonary and coronary vascular resistance accompanied by systemic arterial hypotension.

3 Cardiac output increased and coronary blood flow increased in those animals with a normal or low resting coronary flow and decreased in those with high resting coronary blood flow.

4 The depletion of catecholamine through the administration of reserpine does not change the response basically although it is modified slightly.

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Electrical and anatomic study of the Purkinje system of the canine heart

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The new possibilities for investigation made available by recording electrical potentials directly from various portions of the conduction system of the intact heart were suggested by Sodi Pallares and co-workers.[1] Since then investigation related to the subject has resulted in several excellent studies.[2-4] Especially relevant to this report are the extensive studies of Venerose and associates[3] in regard to activation of subendocardial Purkinje and muscle fibers of the left septal surface.

This paper provides further information in regard to the electrical and anatomic distribution of the peripheral ventricular conduction system Specifically this study was undertaken to obtain information in regard to the following (1) Since intravital staining with iodine of the subendocardial Purkinje system (Fig 1) demonstrates this to be a network of fine interconnecting strands is it possible to record Purkinje (arborization) potentials localized to these strands as differentiated from the intervening endocardium? Previous studies[2-4] have localized Purkinje potentials to the areas known for the distribution of the bundle branches and peripheral network, but the more precise localization to individual strands remains to be determined (2) What are the electrical and anatomic characteristics of the peripheral Purkinje network as related to the earliest sites of activation of the left septal surface? (3) Intravital staining shows a rich supply of conduction tissue over the endocardium of the right ventricular free wall (Fig 1) however Medrano and co-workers[4] could register no Purkinje potentials from the canine right ventricular free wall except in the trabecular zone close to the interventricular septum They concluded that the activation wave in the right ventricular free wall is probably transmitted by nonspecific muscle fibers (rather than by Purkinje tissue) On the other hand Pruitt and Essex[5] have recorded Purkinje potentials from the right ventricular free wall Investigation of this facet of ventricular activation was undertaken in our studies to clarify this problem

Methods

Since this is the first of several reports from our laboratory concerning ventricular activation a rather detailed description of the recording system will be presented. The system has been designed to simulate that reported by Scher and co-workers[6] and the multipolar electrodes were of the

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type used by them. In brief, each electrode consists of fifteen fine tungsten wires assembled around a central shaft. The ends of the recording wires are located approximately 1 mm. apart with a 0.3-mm. maximal diameter of the assembly. The outputs of twelve Type 122 Tektronix preamplifiers are connected to Honeywell power amplifiers, which, in turn, drive M 1650 fluid-damped miniature galvanometers of a twelve-channel Visicorder oscillograph. The frequency response of the galvanometers is flat to 1,000 cycles per second; the Tektronix preamplifiers have an even greater frequency response. All records are obtained at a paper speed of 500 mm. per second. A switch on the amplifier chassis allows unipolar (each terminal against a distant electrode) and bipolar (difference between adjacent points) tracings to be recorded. Another switch allows recording from points 1 through 10 or substitution of points 11 through 15 in place of 6 through 10. Throughout each experiment a Lead II electrocardiogram is monitored on channel 12 and a fixed time reference bipolar lead in the ventricle is recorded on channel 11 (Fig. 2).

Studies were conducted in 15 mongrel dogs which weighed 15 to 20 kilograms. Each dog was anesthetized with intraperitoneal pentobarbital, 30 mg. per kilogram, and artificial respiration was administered via a tracheostomy tube. The chest was opened with a longitudional sternum splitting incision, and the heart was cradled in the pericardium. The reference electrode was inserted into the left ventricle, and a base line tracing was recorded. Multipolar electrodes were then inserted through the free wall of either ventricle. The basal left septal surface usually was reached most easily by directing the electrode through the basal left ventricular wall. The middle and lower portions of the left side of the septum were reached by insertions through the left ventricular free wall or by insertions from the right ventricle across the septum. The low right septal surface was not explored because of the high incidence of complete right bundle branch block noted with such insertions in our preliminary studies. Monitoring the deflections made it possible to determine when the electrode was located properly for recording from points in the cavity and adjacent points in the septum or free wall—subendocardium and deeper ventricular muscle. The deflection from each point (50 mv. 1.5 cm.) then was increased tenfold to fifteen fold, in order to detect Purkinje potentials. Injury potentials disappeared in 3 to 5 minutes, as has been noted by Scher and associates and by Durrer and van der Tweel[7] in their studies using a plunge electrode. In our

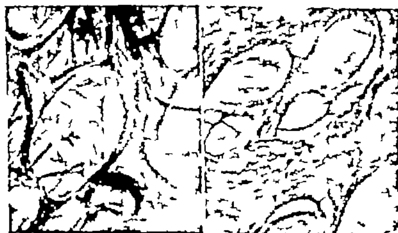


Fig. 1. Peripheral Purkinje system over the subendocardial surface of the left ventricular septal surface (*left*) and the right ventricular free wall (*right*). Note the latticework appearance of the conduction tissue, with islands of endocardium encompassed by the Purkinje strands.

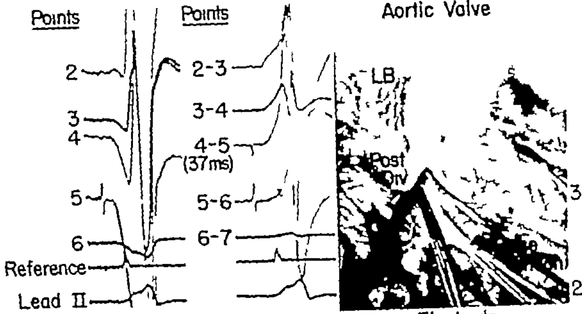


Fig 2 Purkinje potential recorded from electrode 1 in the proximal portion of the posterior division of the main left bundle The electrode was inserted through the basal left ventricular free wall into the septum. Unipolar recording demonstrates that the Purkinje potential could be recorded only from point 3 and it occurred 20.8 msec prior to activation of the bipolar reference point Bipolar recording demonstrates the Purkinje potential between points 4-5 and 5-6 It occurred 20.0 msec prior to activation of the reference point. The Purkinje-muscle activation interval (P M interval) is 37 msec Iodine staining of the endocardium demonstrated electrode 1 penetrated conduction tissue Electrodes 2 and 3 did not penetrate conduction tissue, and Purkinje potential could not be recorded from these insertions. Electrode 2 penetrated the endocardial surface 0.5 mm from the posterior division of the left bundle

studies, 10 to 20 electrodes were inserted into each heart

At the conclusion of each experiment the electrodes were passed completely through the heart or a fine thread was attached to the electrode and pulled through the electrode tract The endocardium then was stained with Lugol's solution and photographed

Interpretation of records The timing of Purkinje potentials and local activation times of bipolar records were taken as the peak or nadir of monophasic complexes. With diphasic complexes the instant at which the intrinsic deflection crossed the isoelectric line was used Durrer[7] has presented a detailed discussion of the criteria for acceptance of such tracings. The deflection of the bipolar record indicates the direction of spread of activity and the convention used here was that described by Scher[4] (a negative deflection indicates spread away from the tip of the electrode) Approximately 3 000 measurements from 145 insertions form the basis for the results presented

Results

A total of 145 insertions yielded 122 recordings without muscle injury currents from the subendocardial area Of the 23 unacceptable tracings, 15 were from the right ventricular free wall Iodine staining of the endocardium demonstrated that 75 electrode insertions had penetrated conduction tissue and of these 61 (81 per cent) had recorded Purkinje potentials.

Left ventricular septal surface On the upper one third of the left septal surface Purkinje potentials were recorded only from those electrodes which were in direct contact with the left bundle or strands of

interconnecting Purkinje fibers The earliest Purkinje potentials were recorded from the main branch of the left bundle after it emerged beneath the aortic valve. These potentials could not be recorded except when the insertion was in direct contact with the left bundle. Fig 2 demonstrates Purkinje potentials recorded from the proximal portion of the posterior division of the left bundle and the electrode position of this insertion Shown in addition is an accompanying electrode, 0.5 mm from the bundle branch from which no Purkinje potentials could be recorded. In one heart in which there was an accessory branch that emerged apart from the left bundle, a fortuitous insertion permitted recording of a Purkinje potential from this strand (Fig 3) In our studies over the past 3 years involving iodine staining of the conduction system we have noted such an accessory bundle in 9 of 90 canine hearts.

Over the upper one third of the septum Purkinje potentials could be recorded only to a depth of 1 or 2 mm beneath the endocardial surface Also the time intervals between the activation of Purkinje tissue and the activation of adjacent muscle fibers (P M interval) were the greatest intervals noted (14 to 60 msec) Purkinje potentials were recorded with increasing frequency as the insertions progressed from base to apex. The Purkinje–adjacent muscle activation time interval shortened with this progression as found by Venerose and associates. The earliest sites of muscle activation were found in the middle of the left septal surface 1 0 to 1.5 cm. below the bifurcation of the left bundle. Purkinje potentials recorded in the area above these early activation sites, yet located below the bifurcation of the left bundle could be recorded only to a depth of 1 to 2 mm Fig 4 illustrates the Purkinje potentials recorded in this area and shows a P M interval of approximately 15 msec.

On the lower two thirds of the left septal surface 20 insertions revealed Purkinje potentials. In all but 3 of these the electrode penetrated strands of conduction

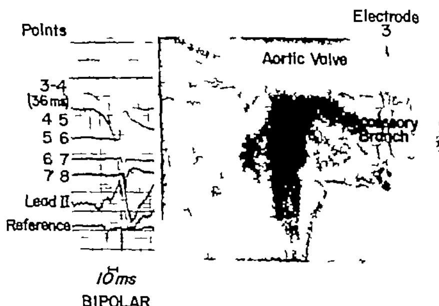


Fig 3 Purkinje potential recorded from an accessory branch that emerged part from the main left bundle. Bipolar tracing show P M interval of 36 msec Lead II indicates right bundle branch block, which had developed prior to the above recording The electrode was inserted from the right ventricular free wall through the septum. Iodine staining of the endocardium demonstrated the electrode to penetrate the fine strand of conduction tissue which emerged beneath the aortic valve part from the main left bundle

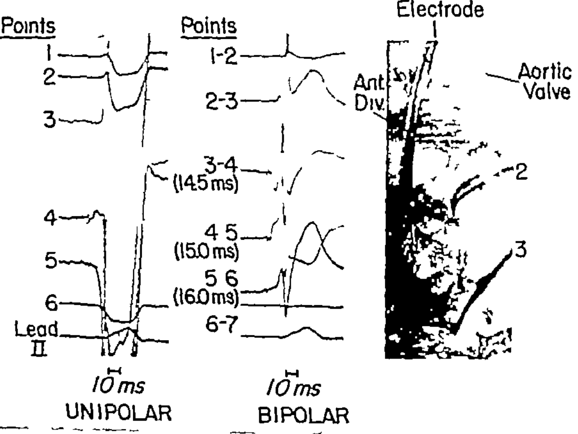


Fig. 4. Recording from positions in the area 1.5 cm. below the bifurcation of the main left bundle. The electrodes were inserted through the left ventricular free wall into the septum. The Purkinje potentials demonstrated were recorded from electrode 1. No such potentials were recorded from electrode 2, but were recorded from a single point on electrode 3. Iodine staining demonstrated electrode 1 to be in contact with a very fine strand of conduction tissue which extended into the island of clear endocardium; electrode 2 was not in contact with Purkinje tissue and electrode 3 penetrated a well-defined strand of Purkinje fibers. Unipolar recording demonstrated Purkinje potentials on points 4 and 5. Point 6 was located in the cavity. Bipolar recording demonstrated Purkinje potentials between points 3-4, 4-5 and 5-6. The P M intervals are shown. Note absence of deflection on points 6-7 indicating that these points were in the cavity.

tissue. These 3 positions were located 0.5 to 1.0 mm. from visible interconnecting strands. Twelve positions from which no potentials were recorded were located in islands of endocardium surrounded by the conduction system network. An additional 6 electrode tracts penetrated strands of conduction tissue, yet no Purkinje potentials were recorded from these sites.

In the middle of the left septum (area of earliest activation) and toward the apex Purkinje potentials were recorded at increasing depths beneath the septal surface. In the mid and lower septal areas these potentials usually were recorded to a depth of 3 to 4 mm.; the deepest penetration found was 4 mm. An analysis of the intervals between Purkinje potentials and adjacent muscle activation (P M interval) in the mid and lower left septum found that they varied between 2.8 and 10.0 msec. (average 6.0 msec.). In those insertions (20 recordings) which recorded Purkinje potentials to a depth of 3 to 4 mm. beneath the endocardial surface, the P M intervals were consistently shorter at a depth of 2 to 3 mm. than at the endocardial surface as shown in Fig. 5,A. In addition, muscle activation at such deeper points occurred earlier than that at the surface, and bipolar leads showed the activation wave to move toward the endocardium or demonstrated reversal points (diphasic deflections) nearer the endocardial surface. Insertions in this

area which demonstrated no Purkinje potentials, or recorded these to a depth of 1 to 2 mm. revealed no such consistent activation pattern in the subendocardium.

Left ventricular free wall. In the left ventricular free wall 15 positions recorded Purkinje potentials all of these insertions had penetrated strands of conduction tissue. Three penetrated conduction tissue but no arborization potentials had been recorded. Ten positions without such potentials were not in contact with conduction tissue.

Purkinje potentials could be recorded only from the middle of the left ventricular free wall and anterior wall adjacent to the septum (areas without underlying papillary muscle). No potentials were recorded from the basal free wall. The depth of penetration of arborization potentials was consistently 2 to 3 mm beneath the endocardial surface as noted by Sodi Pallares and associates,[4] with P M intervals varying from 4.4 to 10.8 msec. (average, 8.3 msec.) Muscle activation in areas in which Purkinje potentials were recorded consistently occurred 0.7 to 3.8 msec. earlier at a depth of 2 to 3 mm than at the endocardial surface as illustrated in Fig. 5 C.

Purkinje potentials recorded in the free

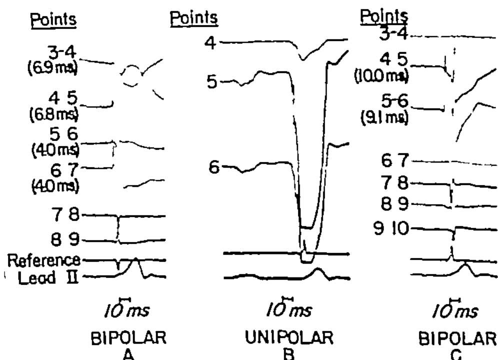


Fig. 5. *A*, Bipolar recording from electrode penetration into the middle left septal surface from the right side. The upright deflections in the upper two tracings indicate spread of activation toward the endocardial surface from 3 mm. beneath the surface (points 3-5). Timing of muscle activation from reference bipolar tracing: points *3-4* +2.0 msec.; *4-5* +2.0 msec.; *5-6* 0 msec.; *6-7* 0 msec. The P M intervals are indicated above beneath the electrode points. The recording between points 7-8 and 8-9 demonstrated no Purkinje potentials, and their amplification was decreased for the above recording. *B*, Unipolar recording of Purkinje potentials from points 5 and 6 of an electrode in the left ventricular free wall. Note that the arborization potentials occurred on the downstroke of the main ventricular deflection at 10.0 msec. before activation of the reference point. *C*, Bipolar recording of the same insertion shown in *B*. Upright deflection recorded between points 4-5 indicates spread of activation toward the endocardial surface. Timing of muscle activation from reference electrode: points *4-5* +1.0 msec.; *5-6* 0 msec. The P M intervals are indicated above. In this insertion no Purkinje potentials were recorded deeper than 2 mm (points 5-6). The Purkinje potentials occurred 9.0 msec. prior to the reference electrode activation (10.0 msec. on unipolar recording in *B*).

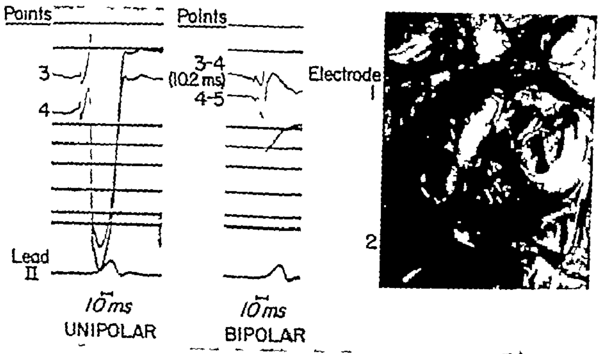


Fig. 6. Recording from the middle of the right ventricular free wall. Unipolar tracing shows Purkinje potential from points 3 and 4 of electrode 2. Bipolar tracing shows P-M interval of 10.0 msec. (points 3-4). Note injury current recording between points 4-5. Iodine staining showed electrode 2 to penetrate a fine network of conduction tissue. Electrode 1 also recorded Purkinje potentials and was located in contact with the border of strand of Purkinje tissue.

wall occurred later than those of the septum and on unipolar tracings were inscribed on the downstroke of the main ventricular deflection (Fig. 5,B) whereas such potentials from the left septal surface occurred before or at the onset of this main deflection.

Right ventricular free wall. Of all the areas studied, persistent muscle injury currents were most commonly encountered in the subendocardial area (1 to 2 mm. depth) of the right ventricular free wall (Fig. 6). From the 40 insertions in this area adequate highly amplified tracings from points in the subendocardium were obtained in 25 instances. Of these, 15 demonstrated Purkinje potentials 1 to 2 mm. in depth from the endocardial surface. Often such potentials were recorded with unipolar tracings in the presence of muscle injury current which was more marked on unacceptable bipolar tracings. The P-M interval varied from 4.8 to 10.0 msec. (average 6.2 msec.). All except one insertion in the right ventricular free wall showed muscle activation to occur in an epicardial direction from the endocardial surface (no reversal points). Also the P-M interval at the endocardial surface consistently was 0.6 to 2.0 msec. shorter than in areas 1 to 2 mm. under the surface. Likewise, the adjacent muscle activation 1 to 2 mm. under the endocardial surface consistently occurred 0.2 to 2.6 msec. after activation of the surface. This contrasts to the findings noted in the subendocardial area of the lower left septum and left ventricular free wall.

Over the right ventricular free wall all electrodes which recorded Purkinje potentials penetrated strands of Purkinje tissue. Of the 10 insertions which recorded no Purkinje potentials, 5 were in areas free of conduction tissue and 5 had penetrated such tissue.

Discussion

A word is in order concerning the use of plunge electrodes for this type of study. Alanís and associates have suggested that such electrodes often, if not always, are associated with local injury and local

Table I

Case	Age Sex	Height	Body build	Diagnosis	Preformula weight (lb.)	Postformula Weight (lb.)	Postformula Days	Digitalis	Diuretics
1	72 M	5'11	L	A.S.H.D., congestive failure, diabetes mellitus, obesity, gout	215½	202½ 198½ 187½	2 4 50	P	P
2	83 M	6	L	A.S.H.D., recent myocardial infarction, congestive failure, obesity	216½	203½ 198½ 195½	7 22 38	P	P
3	53 M	5'11½	L	H.H.D., congestive failure, osteoarthritis, obesity	249	236 234½ 222½ 210 200½	5 13 40 74 102	0	M(×1)
4	69 M	6	L	A.S.H.D., recent myocardial infarction, congestive failure, obesity	207½	201½ 193½ 191	4 19 49	0	P
5	78 F	5'4	M	H.H.D. and A.S.H.D., recurrent congestive failure, diabetes mellitus	138	134½ 131½	1 10	P	P M(×1)
6	65 F	5'4	M	A.S.H.D., previous myocardial infarction, acute pulmonary edema	132	125	3	P	C M(×1)
7	59 M	5'8	L	R.H.D., aortic stenosis, mitral insufficiency, coronary insufficiency, congestive failure, obesity, diabetes mellitus, subsequent myocardial infarction	213	209½ 206	7 15	0	M(×1)
8	78 F	5'3	M	A.S.H.D., auricular fibrillation, left bundle branch block, congestive failure	(1)132 (2)134 (3)145	129½ 128½ 131 136 131 145	2 6 4 1 2 15	I P P	P M(×1) P M(×1)

Included subsequent hypocaloric or sodium-poor diet.
A.S.H.D. Arteriosclerotic heart disease. H.H.D. Hypertensive heart disease. R.H.D. Rheumatic heart disease. S. Small frame ... constant oral diuretics with formula. M(×1) One mercurial injection with formula. (Table I is continued on page 36.)

A number of these patients had been taking oral diuretic agents at the time their congestive failure recurred. In most instances the dose was increased. A single injection of a mercurial diuretic was administered initially to the majority of patients when they presented with moderate or advanced congestive failure. On the other hand, a marked diuresis was achieved in several edematous patients in whom diuretics and spironolactone were purposely withheld.

Sedation and other supportive measures were prescribed as indicated. Previous

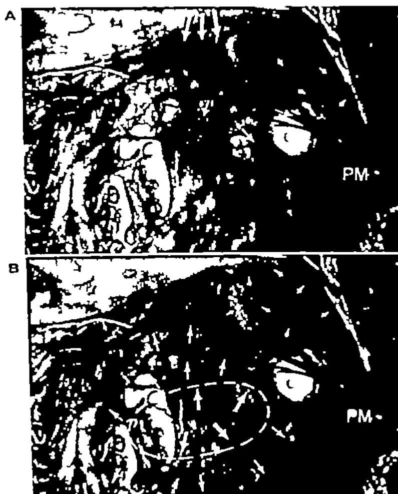


Fig 7 Sequence of activation of the Purkinje conduction system (*A*) and of the left ventricular septal surface (*B*). Large arrows indicate earliest activation, medium-sized arrows indicate intermediate timing and small arrows indicate the latest activation time. PM Papillary muscle *A* The sequence shown indicates that the conduction system impulse spreads over small strands of the arborization network in a base-to-apex direction and laterally to the left ventricular free wall *B* Muscle activation of the left septal surface begins in the middle of the septum (*encircled area*), 1.0 to 1.5 cm. below the bifurcation of the main left bundle branch The spread of activation is in an apex-to-base direction in the intervening area between the bifurcation of the left bundle and the earliest sites of activation suggests that activation is through nonspecific muscle fibers rather than by the arborizations of the conduction tissue in this area.

conduction block. Conversely Durrer and van der Tweel set forth strong arguments in support of the assumption that the effects of injury do not significantly affect the results of such studies. At the present stage of instrumentation it is only with the use of such electrodes that areas beneath the endocardial surface can be explored In our study of the 75 insertions which penetrated conduction tissue as demonstrated by iodine staining of the endocardium 61 (81 per cent) demonstrated Purkinje potentials. All of the points which penetrated conduction tissue without demonstration of Purkinje potentials were located in the lower left septal mass or right ventricular free wall (areas of fine arborization of the Purkinje system) This suggests that the electrode did cause focal conduction block in these in

sections is discussed by Amer and coworkers. However once a Purkinje potential could be recorded it remained present for prolonged periods of time In 3 dogs arborization potentials were recorded in the lower left septal surface for a period of 6 hours without change in configuration or timing

The question arises as to how one can be certain that iodine staining is demonstrating the conduction system Over the past 4 years we have made over 4 000 serial sections for histologic study in hearts subjected to iodine staining From these studies we have become convinced that iodine staining accurately demonstrates the peripheral conduction system at the endocardial surface (preferential staining of fibers with higher glycogen content than cardiac muscle)

The timing of Purkinje potentials in our study shows that the impulse travels down the left bundle and upper interconnecting small septal strands and spreads over the arborization network of the lower septal surface to the left ventricular free wall No late Purkinje potentials were recorded from the upper left septal surface This contrasts with the findings of Venerose and associates who stated that the latest activity in Purkinje fibers was recorded from fibers located at the base of the septum beneath the aortic and mitral annulae However these authors point out that in iodine-stained specimens no Purkinje fibers were located in these areas As noted we were not able to record Purkinje potentials in these areas free of conduction tissue Previous studies have consistently shown that the first muscle region to become activated on the left septal surface is in the middle third (Fig 7)[3,4] This area has been identified previously as being located at the bifurcation of the main left bundle In our studies this area was located 1 0 to 1.5 cm below the bifurcation of the left bundle and the intervening area is covered with a latticework of Purkinje tissue. Timing of surface muscle activation indicated that the excitation wave spread in an apex to-base direction in this intervening area This suggests that the activation wave in this area is by propagation through nonspecific muscle fibers as proposed by Sodi Pallares[1] for the high positions of the left septum

It is interesting to speculate why the electrical impulse traverses the fine strands of Purkinje tissue for the distance of 1 0 to 1 5 cm beneath the bifurcation of the left bundle before initiating muscle activation in the middle of the septum One possibility is that excitation may fail to enter penetrating muscle branches in the area immediately below the bifurcation of the left bundle Hoffman[12] has mentioned that although conclusive experimental demonstration is lacking it is likely that excitation may enter some branches of the Purkinje system and fail to enter others.

In our studies the location of the earliest sites of activation in the middle left septal surface correlated well with the areas in which Purkinje potentials could be recorded to varying depths beneath the endocardial surface No such potentials could be recorded 3 to 4 mm beneath the septal surface in areas above the middle third of the septum From these data it is suggested that the muscular activation process begins in the mid septal surface because the conduction system begins to penetrate the septum in this area. Uhley and Rivkin[13] in their studies of iodine staining of the conduction system considered that the concentration of conduction tissue visible on the left septal surface correlated with the earliest sites of muscle activation We were unable to confirm their assumption In our iodine-staining studies. In addition our results suggest that in the mid and lower left septum where Purkinje potentials penetrate 3 to 4 mm below the surface the area in which the process of muscle activation begins is approximately 3 mm beneath the endocardial surface. A similar conclusion is suggested for areas of the left ventricular free wall where arborization potentials can be recorded 2 to 3 mm below the endocardial surface. Such insertions consistently demonstrated that, 2 to 3 mm beneath the endocardial surface muscle activation began 0 7 to 3 8 msec. earlier than at the endocardial surface In the right ventricular free wall the shortest P M intervals were at the endocardial surface (rather than 1 to 2 mm

under the surface) and the timing of muscle activation indicated that activation began at the endocardial surface.

The general pattern of left ventricular septal activation of the Purkinje system and adjacent muscle of the subendocardium as indicated in our studies, is illustrated in Fig. 7. As noted previously, the lower right septal surface was not explored because of the high incidence of right bundle branch block. This area was included in the studies of Medrano and co-workers. Our results are consistent with the findings of these authors, except in regard to the right ventricular free wall. They concluded that the activation wave in the right ventricular free wall probably is transmitted through nonspecific muscle fibers. Our data, with the demonstration of Purkinje potentials in this area, suggest that the activation wave to the right ventricular free wall is spread by the conduction system.

Summary

The activation of the conduction system and adjacent muscle of the subendocardium of the entire left ventricle and right ventricular free wall has been studied in the intact canine heart by means of plunge electrodes. Penetration of Purkinje potentials to a depth of 3 to 4 mm. beneath the endocardial surface was recorded first in mid left septal surface areas of early muscle activation (1.0 to 1.5 cm. below the bifurcation of the left bundle). No such penetration occurred in the upper left septal surface. A shorter Purkinje–adjacent muscle activation time and earlier muscle activation 2 to 3 mm. below the endocardial surface as compared to that at the surface suggests that muscle activation begins at this depth in the lower left septal surface and left ventricular free wall. Purkinje potentials recorded in the right ventricular free wall indicate that the activation wave to this area is transmitted by the peripheral conduction system. There was 81 per cent correlation of the localization of specific strands of conduction tissue demonstrated by iodine staining with the recording sites which demonstrated Purkinje potentials.

We are indebted to Dr. Allen M. Scher, Department of Biophysics and Physiology, University of Washington School of Medicine, Seattle, Wash., for the time spent with one of the authors (M.S.S.) in his laboratory and for his advice in regard to the construction of our recording system. We are also indebted to Mr. Otis Brown for supplying the multipolar electrodes used in this study. The valuable technical assistance of Mr. O. R. Lipscomb, Jr., during the course of this study is most appreciated.

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Intrapericardial teratoma

Report of a case

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The intrapericardial location of a teratoma of the adult type is uncommon. There have been 4 cases reported in the world literature and all of those were seen in children. We are adding to these a recent observation of our own not only because of the rarity of these strictly intrapericardial teratomas but also because of their challenging surgical interest.

Case report

R. J. N. (N. 341 120) was an infant who was admitted to the Buffalo Children Hospital at 1 day of age because of extreme cardiomegaly. When she was 3 hours old respiratory distress and cyanosis had been noted. A roentgenogram of the chest revealed marked cardiomegaly and the patient was transferred to this hospital.

She was a well-developed, but desperately ill infant in acute respiratory distress, with grunting respirations and flaring of the alae nasi. The apical pulse was 132, the respirations were 74 and the weight was 3.0 kilograms. The infant was only mildly cyanotic in oxygen, but markedly so when crying. Peripheral pulses were present and there was no evidence of edema. The lungs were clear to auscultation. The heart had a regular rhythm, and no murmurs were heard. The liver was 1 cm. below the right costal margin.

The hemogram and urinalysis were normal. The chest roentgenogram showed a markedly enlarged cardiac silhouette which filled almost the entire thorax, with only a small amount of aerated lung posteriorly (Fig. 1). An electrocardiogram revealed a qR pattern in Lead V1.

On the day after admission the patient underwent catheterization of the right side of the heart and cineangiography. The catheter was passed from right to left at the atrial level through a patent foramen ovale and all chambers of the heart were entered. The cineangiography revealed an anterior mediastinal mass with areas of calcification which compressed the right atrium and pulmonary arteries and displaced the heart and great vessels posteriorly and to the left. There was no evidence of an intracardiac shunt; the peripheral arterial oxygen saturation was 55 per cent without and 98 per cent with oxygen administration. The venous and right atrial mean pressures were elevated. After cardiac catheterization convulsive movements were noted. An exploratory thoracotomy was then performed.

The chest was entered through a right anterolateral paracostal incision at the fourth intercostal space. The right lung was seen to be atelectatic and the pericardial sac bulged forward. Opening of the pericardium exposed a large nodular tumor. The tumor seemed to lie upon the right atrium, the pulmonary artery and the base of the aorta. These cardiovascular structures were compressed posteriorly and to the left. The tumor was three times the size of the heart, measured approximately 8 by 12 cm. and arose from a small pedicle at the base of the ascending aorta. When the dissection was being carried inferiorly and the tumor mass elevated from its bed, the aorta ruptured and hemorrhage ensued. The heartbeat, which had been weak during the surgical procedure, stopped at this point and could not be restored.

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Fig. 1. *Left.* Roentgenogram of the chest on admission. *Right.* Lateral projection which shows area of calcification.



Fig. 2. Anterior view of the undissected heart and lungs with the pericardium reflected superiorly shows size-relationship to the surgically removed teratoma (*on the right*). Magnification ×1

Pathology. The surgically removed tumor was received in fixed state. It was somewhat pear shaped, had a lobulated surface, weighed 51 grams, and measured 6.2 by 5 by 3.5 cm. The mass was well encapsulated with a smooth surface, except for an area of 2 by 1.5 cm., where the capsule was missing, corresponding to the site of attachment of the tumor to the ascending aorta. There were a few pea-sized protrusions, some solid and some cystic (Fig. 2). The cut surface showed a fairly characteristic picture of a benign polycystic teratoma. The cysts varied in size from 2 to 10 mm. In the more firm central portion of the tumor several areas of cartilage, some of which were slightly calcified, could be seen alternating with fairly firm grayish-white but seemingly well-encapsulated, parenchymatous portions. These, in turn, were intimately surrounded by more loose grayish tis-

The syndrome of compression of the pulmonary artery by an aneurysm of the ascending aorta

A case report

T P Kulkarni M S
*M J Gandhi M D***
*K K Datey B A M D F R C P (Edin) M R C P (Lond) F A C C (U S A) D T M & H (Lond) D C H (Eng) F C C P (U S A) F I C A****
Bombay India

Aneurysms of the ascending aorta and arch may present varied manifestations depending upon whether the structures compressed by the aneurysm are the blood vessels, nerves trachea esophagus or different chambers of the heart

The main pulmonary artery and the proximal parts of its major branches closely entwine around the ascending aorta and the arch particularly in the concave aspects. By its mere proximity an aortic aneurysm can cause progressive compression and narrowing of the pulmonary artery producing chronic cor pulmonale It is rather surprising how infrequently this syndrome has been recognized clinically So far only about 93 cases of this syndrome have been recorded in the literature and the majority of them have been detected at autopsy [1-4] The syndrome closely but imperfectly mimics many common cardiovascular disorders and thus presents a diagnostic problem It is our purpose to report here a case and to emphasize that with greater awareness this syndrome can be diagnosed clinically This is particularly important today since it may be possible to help such a patient surgically

Case report

A 30-year-old Muslim male was admitted to the K.E.M Hospital, Bombay for progressive exertional dyspnea and frequent attacks of a productive cough which had been present for 9 months. He felt breathless after walking about 50 yards on the level and on climbing a few steps. He denied any history of rheumatic fever or syphilis.

On examination, he had early signs of congestive cardiac failure. There was no cyanosis or clubbing The blood pressure was 100/50 mm. Hg The apex beat was in the fifth left intercostal space in the anterior axillary line and was hyperdynamic in character There was no parasternal heave A systolic thrill and Grade 3 systolic murmur as well as a faint early diastolic murmur were heard at the left sternal edge in the third intercostal space. The second sound was single.

A phonocardiogram recorded at the base of the heart showed a high-frequency systolic murmur that extended up to the aortic component of the second sound. The pulmonary component was very feeble and followed the aortic component by 0 05 second. There was a short early diastolic murmur

Blood V D R.L. was strongly positive 4 plus.

A plain skiagram of the chest revealed a en

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Fig. 1. *Left.* Roentgenogram of the chest on admission. *Right.* Lateral projection which shows area of calcification.

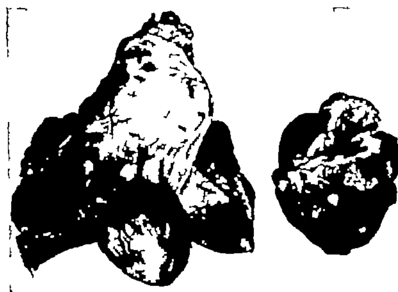


Fig. 2. Anterior view of the undissected heart and lungs with the pericardium reflected superiorly shows size-relationship to the surgically removed teratoma (*on the right*). Magnification ×1.

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Fig. 3 Cut surface of the tumor magnification × 2. Note the cysts at the periphery and the large solid mass of tissue (glia) the enter



Fig. 4 Low power photomicrograph which shows cyst lined by stratified squamous epithelium well as island of cartilage nd bundles of m scle th ue I the pper right glia Hematoxylin-eosin, ×100.

sue Some of the larger cy contained colloid like material others more serous or mucoid secretion (Fig 3)

Microscopically the t mor showed the ha acteristic f tures of a d lt ter toma, with deriv tives of all three germinal layers particularl of neural ectoderm nd of entoderm (Fig 4). There ere cy tic ities lined by stratified squamous epithelium in sever l re there w neuroglial t ue with are neu ells. There were lso ma y cyst lined by mucosal urface with gland simila to pyloric gland (Fig 5) There were scattered groups of serous and mixed mucoserous glands. Ducts were also seen a few lined by stratified polyhedral cells with brush borders. Respiratory epithelium with cartilage was found in the walls of some. In addition there were areas with well-formed bone marrow as well a groups of smooth muscle, striated and heart muscle fibers.

At necropsy the pericardial sac was markedly distended and there were recent suffusions, mostly on its inner surface. There were no anomalies of the heart. The ductus Botalli was patent although slightly constricted in one portion, with the intima I typical wri kled state The foramen ovale was compensated when stretched, in the fixed specimen about 1 cm. in diameter Death had been caused by laceration of the orta in the process of removal of the tumor from its seemingly firm ttachment t the base of the heart.

Comments

Cardiac catheterization with cineangiography demonstrated an anterior mediastinal mass with areas of calcification which produced a filling defect on right atrial opacification and was associated with elevation of the mean right atrial and venous pressures. A similar filling defect has been reported previously

Histologically our case was that of a typical congenital polycystic teratoma which contained fully differentiated tissues derived from all three germinal layers including particularly the neural ectodermal A feature in common with the cases previously described was the attach



Fig 5 Photomicrograph showing in the ent glandula tructures which resemble the pyl region surrounded by glial t sue Hem t xylin eosin, ×450

ment of the tumor by a short pedicle to the adventitia at the base of the ascending aorta. Some authors have emphasized that this is extremely important since damage to the aortic wall which may cause fatal hemorrhages can be produced during operation. This happened in our case which in this matter resembles closely the case reported by Gebauer.

Dabbs and associates, after reviewing the literature with careful study of the histologic description came to the conclusion that some cases mistakenly referred to in the literature as intrapericardial teratoma were bronchogenic cysts and not teratomas at all. This is true of the case of Joel[6] and of those reported by Jellen and Fisher and Basora Defillo and Lichtenberg.

As to the case reported by Grimm, even if the histologic description by the author fits that of a teratoma the relationship between heart and tumor as given in the report is not stated with sufficient clarity. For this reason we believe that Grimm's case cannot be included in any comparative discussion of intrapericardial teratomas.

It seems to us that the first well-documented case of intrapericardial teratoma was reported by Gebauer[1] in 1942. The other 3 cases were those of Willis,[2] Claireaux, and of Richards and Reeves. Of particular interest is that the case reported by *Richards and Reeves* was the only one in which a successful operation was carried out.

Summary

A typical case of an adult type of intrapericardial teratoma is reported. A review of the literature disclosed only 4 well documented cases. Attention is called to the intimate attachment of the teratoma to the aortic wall and the inherent danger of hemorrhage during surgical removal of the tumor.

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The syndrome of compression of the pulmonary artery by an aneurysm of the ascending aorta

A case report

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Aneurysms of the ascending aorta and arch may present varied manifestations depending upon whether the structures compressed by the aneurysm are the blood vessels, nerves trachea esophagus or different chambers of the heart

The main pulmonary artery and the proximal parts of its major branches closely entwine around the ascending aorta and the arch particularly in the concave aspects. By its mere proximity an aortic aneurysm can cause progressive compression and narrowing of the pulmonary artery producing chronic cor pulmonale It is rather surprising how infrequently this syndrome has been recognized clinically So far only about 93 cases of this syndrome have been recorded in the literature and the majority of them have been detected at autopsy [1-4] The syndrome closely but imperfectly mimics many common cardiovascular disorders and thus presents a diagnostic problem It is our purpose to report here a case and to emphasize that with greater awareness this syndrome can be diagnosed cl nically This is particularly important today since it may be possible to help such a patient surgically

Case report

A 30-year-old Muslim male was dmitted t the K.E.M Hospital, Bombay for progressiv ex ertional dy pnea nd frequent ttacks of productive cough which had been present for 9 months. He felt breathless after walking about 50 yard on the level and on climbing few steps. H denied any history of rheumatic fever or yphilis.

On examination, he had early signs of congesti cardiac failure. There was no cyanosis or clubbing The blood pressure was 100/50 mm. Hg The pex beat wa in the fifth left intercostal space I the terior axillary l ne and wa hyperdynamic in character There wa no para ternal hea e. A systolic thrill and a Grade 3 systolic murm well faint early diast lic murmur were heard t the left sternal edge in the third intercostal space. The second sound was single

A phonocardiogram recorded t the base of the heart howed high-frequency sy tolic murmu that extended p to the aortic component of the second sound. The pulmonary component was ery feeble and followed the aortic component by 0 05 second. There wa short early diastolic murmur

Blood V D R.L. wa strongly positiv 4 plus.

A plain skiagram of the hest revealed en-

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Spirono-lactone	*Adreno-cortical steroids*	*Clinical features*
0	0	See text
0	0	See text
0	0	See text
0	0	See text
0	0	Progressive congestive failure while on maintenance digitalis, hydrochlorothiazide, and salt restriction. Diabetes controlled with 18 its of NPH insulin. Given only one mercurial injection at onset of formula therapy Comparable diuresis during second bout of congestive failure. Fasting blood sugar levels and diabetic status remained relatively unchanged while on formula
0	0	See text
0	0	Prompt diuresis nd loss of congestive symptoms after formula and single mercurial injection for initial bout of failure. Acut myocardial infarction 4 months later sub-sequent gain in weight to 209½ pounds during convalescence. Resumption of formula and interval feedings to control hypoglycemic symptoms. Weight decreased to 197 pound in 27 days, and to 195½ pounds in 38 days
0	0	Repeated congestive failure with prompt diuresis and amelioration of epigastric tenderness and dyspnea—even after oral diuretics, digitalis, and dexamethasone did not suffice. Potentiated diuretic response when spironolactone was added
0	P	
+	P	

M: Medium frame. L: Large frame. (1), (2) (3) First, second, or third bout of congestive failure. P Pre-formula therapy C Con-

medication for unrelated disorders (e.g hormone therapy insulin parenteral vita m n B_1) generally was continued without alteration. It was necessary to resort to thoracentesis only in Case 13 (a patient with anasarca due to widespread malig nancy)

The details of dietetic management n achieving and maintaining weight reduc tion are similar to those which I have previously reported.[7] It will suffice to point out that such a program is arbitrarily divided into the following three phases *Phase I*—consisting of formula as the chief

Fig 1 Position of tip of i tracardiac catheter t the site of the obstruction.

DPA (Withdrawal on 88 F hr Valve) RV

Fig 2 I tracardiac thdra al pressure pulse tracing, from the pulmonary artery to the right entricle.

larged cardiac silhouett There was convexity in the region of the pulmonary artery The pulmonary *ascular fields, especially on the right side* appeared to be hypovascular The electrocardiogram showed right axis deviation, ertical position of the heart, and biventricular hypertrophy

O catheterization of the right side of the heart the outflow tract of the right entricle ppeared t be displaced t the left the catheter could be negotiated easily in the left pulmonary rtery How *ever several ttempt to push the tip of the catheter* int the right pulmonary artery failed. The progress of the ca heter in this direction seemed to be blocked and the catheter turned every time t this point and entered the left pulmonary artery (Fig 1). The patient was placed in the left terior oblique position, and nder fluoroscopic control the tip of the catheter as directed toward the right pulmonary artery but I seemed to impinge against lgenously pulsatile swelling The main and left pulmonary arterial pressures were 25/7 mm. Hg

The right entricula pressure w 88/7 mm. Hg with systolic pressure gradient of 63 mm. Hg at the pulmonary alv area (Fig 2) Femoral arterial pressure was 110/50 mm. Hg Oxygen satur tion studies did not reveal any shunt. Thus, catheterization of the right side of the heart revealed physiologic narrowing t the pulmonary val e area lth obstruction to the passage of the cardiac catheter into th right pulmonary arterial lumen. The femoral artery tracing suggested aortic incompetence.

Angiocardiography was performed by introducing No. 8 i tracardiac catheter with the tip of the catheter in the right trium and later in the main pulmonary artery The angiocardiograms did not reveal pulmonary alvular stenosis, but showed displacement of the outflow tract of the right entricle to the left, poor nd dela ed filling of the trunk of the right pulmonary artery and dimi ished opacification of the right pulmonary ascular bed (Figs. 3 and 4). Direct percutaneous suprasternal ortography[4] with No. 18-gauge B D needle revealed an aneurysm of the ascending aort i the region of the pulmonary conus, as see on the posteroanterior skiagram (Fig 5) The aneurysm occupied the aortic window (Fig. 6). It was saccular nd originated from the conca aspect of the ascending aorta.

The patient refused surgery and left the hospital

Discussion

This syndrome has been described in the l terature as being very rare and un usual Probably the paucity of reports is due to nadequate clinical recognition of

Fig 3. Angiocardiogram show ng the displacement of the outflow tract to the lef by the neurysm.



Fig 4 Sele pulmona y ngiocardiogram show g poor fill g of he pulmonary tery



Fig 5 Direct supr ternal aortogram (left terior oblique iew) showin the position of the neurysm.

this entity The clinical picture of this syndrome closely *mimics some of* the other clinical conditions (1) Patent ductus arteriosus with pulmonary hypertension These patients can be differentiated by the presence of an accentuated pulmonary component of the second sound and other signs of pulmonary hypertension (2) Pure aortic incompetence (3) Aortic stenosis with incompetence. However the presence of right ventricular hypertrophy single second sound marked enlargement of the pulmonary artery and oligemic lung fields should arouse suspicion of compression of the pulmonary artery (4) Pulmonary stenosis with incompetence. However the presence of left ventricular hypertrophy and wide pulse pressure rules out this condition

Although this syndrome may closely mimic certain commonly recognized cardiovascular anomalies the resemblance is only superficial and this seems to be its main characteristic In a young syphilitic patient with aortic incompetence the presence of right ventricular enlargement either clinically or electrocardiographically and feeble pulmonary component of the second sound are almost diagnostic of this syndrome X ray films of the chest give valuable information and show enlargement of the cardiac silhouette with biventricular enlargement. In spite of the



Fig 6 Direct supr ternal aortog m (left anterior oblique iew t 45 degrees) how g the saccular neurysm occupying the aortic indow

prominence of the pulmonary artery the lung hila and peripheral lung fields appear to be ischemic. A careful study may reveal that ischemia is not uniform and that one of the lung fields, depending on the exact location of aneurysm is more oligemic than the other Demonstration of calcification in the aneurysm may be a useful diagnostic point. Although the aneurysmal shadow may show expansile pulsations, the main branches of the pulmonary artery do not pulsate. Catheterization of the right side of the heart is a useful means of diagnosing this condition. The soft pulmonary artery is compressed more or less uniformly giving cardiac catheterization data which closely mimic those of pulmonary stenosis. However it may not be possible to advance the tip of the catheter into one of the branches, depending upon the exact site of compression. The tip of the catheter appears to pulsate too vigorously in spite of the low pressure in the pulmonary artery

Angiocardiography which delineates the ascending aorta and pulmonary artery clinches the diagnosis. A venous angiocardiogram shows displacement of the outflow tract of the right ventricle to the left and the exact site and extent of the compression of the pulmonary artery whereas an aortogram delineates the size shape and the site of origin of the aneurysm This is particularly well seen in the left anterior oblique view which shows best the aortic window

This syndrome of aneurysm of the ascending aorta pressing on the pulmonary artery is a progressive malady which invariably ends fatally The aneurysm may rupture into the pulmonary artery and produce shunts of varying degrees, depending upon the size of the opening If the shunt is large this may result in rapid flooding of the pulmonary vasculature leading to pulmonary edema and death Since the advent of cardiac bypass and cardioplegia these aneurysms have come into the realm of cardiac surgery so that the exact antemortem diagnosis is importa t

Summary

1 A case is presented of syphilitic saccular aneurysm of the ascending aorta pressing on the pulmonary artery and producing chronic cor pulmonale diagnosed clinically

2 This syndrome clinically presents signs of pulmonic stenosis and aortic incompetence. In a young syphilitic patient with aortic incompetence the presence of right ventricular enlargement clinically or electrocardiographically with feeble pulmonary component of the second sound is highly suggestive of this syndrome. X-ray films of the chest usually reveal biventricular enlargement with apparent *enlargement of the pulmonary artery* and oligemic lung fields. The ischemia however may not be uniform. Catheterization findings in the right side of the heart closely *mimic* those of *pulmonary stenosis* However the displacement of the outflow tract of the right ventricle to the left and vigorous pulsations of the tip of the catheter in spite of low pressure in the pulmonary artery are suggestive. The aortogram clinches the diagnosis.

3 The fact is emphasized that this syndrome is not so rare as is commonly believed and now that corrective surgery is possible this syndrome should be borne in mind whenever some unusual features are present.

Addendum

During the past year we have seen 6 more cases of this and allied syndromes in *our hospital alone. One* case showed pressure on the pulmonary artery in another case there was pressure on the pulmonary artery and left bronchus producing bronchiectasis. Three cases showed rupture of an aortic aneurysm into the pulmonary artery producing pulmonary hypertension and in one case there was sudden rupture of the aorta into the pulmonary artery producing rapid flooding of the lungs with resultant pulmonary edema and death.

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Wandering pacemaker occurring during speech, as a result of paradoxical effect of atropine on the A V node

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Transient nodal rhythm with a decrease in heart rate as a paradoxical effect of the administration of atropine had been first described by Wilson in 1915 and subsequently demonstrated by others.[1-4]

In 1914 Gallavardin noticed that the production of nodal rhythm by ocular pressure is facilitated with the administration of atropine This phenomenon has been variously explained as being due to either a selective action of atropine on the vagal terminations, *which are blocked* earlier in the A V node than in the S-A node or an abnormal response of a hyper excitable A V node to atropine, or a transient vagal imbalance at different levels of the conduction system

When the atropine more or less completely blocks the vagus nerve, the cardiovascular effects are rather constant and the acceleration of the sinus rhythm is consistently reproducible

The case presented below provided a opportunity to study this paradoxical effect of atropine on the A V node and to make some additional observations.

Case report

A 25-year-old white man was admitted to the hospital on Dec 25 1961 complaining of frequent attacks of dizziness, ringing in the right ear blurring of the vision, nausea and episodes of "fast heart beating" He had fainted three times in the previous 6 months while walking in the street, with giddiness and "crack feeling" on the top of his head.

Personal and occupational history as well as the history of medical illness, were noncontributory

On examination the patient was anxious, tense, and apprehensive, repeatedly checking his pulse over his neck and wrist. There were ticklike movements of the face and frequent blinking There was coarse nystagmus on left and right lateral gaze The heart was not enlarged there was normal sinus mechanism, sounds of good quality intensity and duration and no murmurs or gallop were noted.

The pulse rate was 85 per minute, and the blood pressure was 120/64 mm Hg On several occasions an increase in the heart rate to 120 was observed while the patient was lying in bed. The remainder of the physical examination was not remarkable

The electrocardiogram (Fig 1) showed first degree A V block, but otherwise was within normal limits. Roentgenograms of the chest and skull were normal audiogram and electroencephalogram were also normal. Significant laboratory data (Table I) were within normal limits.

The patient remained in bed for most of the time, stating that he found it difficult to walk about because of the attacks of dizziness and tachycardia. He was discharged against advice after having refused pneumoencephalogram

The discharge diagnosis was neurocirculatory asthenia although the remote possibility of brain tumor could not be excluded by the data at hand.

In an attempt to shorten the P R interval, 0.5 mg of atropine sulfate was given intravenously The control rate was 100 per minute, and the control P R measured 0.28 second (Fig 2) After 3 minutes the P R interval was 0.20 second and paradoxically the heart rate was 83 per minute

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Fig. 1 Fourteen-lead electrocardiogram showing first-degree A-V block.

The pacemaker was a lower focus as was manifested by the slower rate and the lower voltage of the P wave. At 10 minutes the rate was 79 per minute and retrograde depolarization of the atria was demonstrated by inverted P waves in Leads II, III, and V_F. The P-R interval was 0.16 second. Whether this represents a low localization of the pacemaker but one that is still above the A-V node or upper nodal rhythm with forward conduction delay is not certain.

To this point nothing is new in this case because this type of paradoxical effect of atropine has been produced on many occasions in the past.

Subsequently it was noticed that when the patient was talking or moving slightly in bed the pacemaker was shifted upward. There was also a slight acceleration of the heart rate. When the patient was ordered to stop talking the pacemaker shifted downward and within two beats, the retrograde depolarization of the atria resumed. Competition of the two pacemakers caused a fusion P wave between these two beats. The same phenomenon was reproduced again and again over a period of 30 minutes. Carotid sinus pressure did not have any effect on the retrograde atrial conduction. One-half hour after the intravenous administration of atropine another 0.5 mg. of atropine was given intravenously because the initial dose was thought not to have caused sufficient atropinization. Thirteen minutes after the second injection the patient complained of dryness of the mouth, the heart rate speeded up, and no shifting of the pacemaker could be reproduced.

Comment

The features of this case are in accord with the well-documented paradoxical action of atropine on the A-V node.

P-R prolongation has been found in patients with neurocirculatory asthenia without heart disease[6,7] as well as in perfectly healthy men.[8,9]

Shifting of the pacemaker to the A-V node and back to the S-A node has been found to occur with changes in the vagal tone as slight as those which occur during

Table I Laboratory findings

Hemoglobin 13.3 Gm. per 100 c.c.
Hematocrit 43%
White blood cells 9,800
Differential normal
Sedimentation rate 6
Urinalysis normal
Fasting blood sugar 94 mg. per 100 c.c.
Blood urea nitrogen 10 mg. per 100
Total protein 7.6 Gm. 100

A/G ratio, 4.8/2.8
Serum calcium, 10.4 mg. per 100 c.c.
Serum phosphorus, 2.1 mg. per 100 c.c.
Alkaline phosphatase 3.9 units (King-Armstrong) per 100 c.c.

Prothrombin time 12.5 sec.
With control 12 sec.
Serum total cholesterol, 221 mg. per 100
Serum electrolytes per 100 c.c.
Sodium 135 mEq.
Potassium 4.9 mEq.
Chloride, 96 mEq.
Protein-bound iodine 4.0 µg per 100 c.c.

VDRL and Kolmer tests nonreactive
Spinal fluid
Opening pressure 140 mm. H_2O
Closing pressure 115 mm. H_2O
Clear sugar 81 mg.
Protein 52 mg. per 100
Chlorides 686 mg. per 100 c.c.

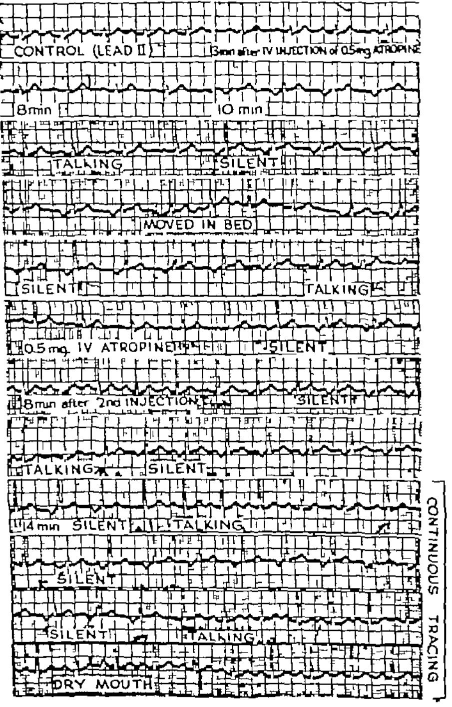


Fig 2 The control tracing shows first-degree AV block. Three and 8 minutes after intravenous administration of 0.5 mg of atropine the heart rate decreases and the PR interval shortens to upper normal limits. Note AV nodal rhythm 10 minutes. Subsequently the rhythm is nodal when the patient is silent, and sinus when he moves slightly in bed or talks. This is well illustrated in the continuous four last strips when the patient alternately talks and keeps silent. In the last strip and thereafter no shifting of the pacemaker is noticed and the patient complained of dryness of the mouth.

respiration or with changes in the position of the body.

To our knowledge the literature contains no previous report of a case in which wandering of the pacemaker was connected with speech. Apparently the atropine caused such a vagal imbalance of the conductive system that minor additional changes, as during talking, were capable of shifting the pacemaker back and forth. When the vagus nerve was completely blocked, no wandering of the pacemaker could be reproduced.

Summary

A case of low atrial or nodal rhythm due to paradoxical effect of atropine is reported whereas slight changes in the vagal tone as with talking were able to cause wandering of the pacemaker.

I wish to express my appreciation to Dr. John A. W... for his ... and assistance in the preparation of this paper.

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Review

Russian research on cardiac compensation and decompensation

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In the past research on cardiac decompensation was largely concerned with hemodynamic functions pathologic changes, and clinical symptoms but more recently biochemical and related structural changes in the myocardium have found increasing attention as shown in the Symposium of the Physiology of Cardiac Muscle in Gorlin's and Bing's articles and particularly in the large volume on cardiac metabolism. Against this background the work of F Z Meerson and associates, at the Institute of Normal and Pathologic Physiology Moscow merits the attention of Western cardiologists. As one of the most comprehensive experimental studies by an single author it includes hemodynamics macroscopic and microscopic structural changes x-ray ECG a d clinical symptoms biochemical changes and energetics and changes in the autonomic and central nervous systems (cardiovascular unconditioned and conditioned reflexes EEG) Meerson studied particularly the compensatory phase (compensatory hyperfunction) in developing left ventricular hypertrophy in the belief that a d tailed stud of cardiac compensation in experimental aortic stenosis would contribut to the understanding of the mechanism (and cause of the ultimate decompensation.

Meerson reviewed his experimental work in two monographs the first and larger one (258 pages) published in November 1960 is devoted mainly to chronic compensation and decompensation with much emphasis on biochemical changes whereas the second one (75 pages) published in 1962 is devoted mainly to acute heart failure with emphasis on hemodynamic changes. In both volumes the results of Western and Russian authors are well integrated. In some aspects recent Western research on cardiac decompensation has paralleled Meerson's work and gives more detailed information. However this does not detract from the merit of Meerson's studies independent confirmation may often be as important as new discoveries.

The bulk of Meerson's work is included in his first book which lists twenty-five experimental papers by Meerson and his associates. Several papers appeared later some of which contain essentially the same information as that in his book, whereas some others, particularly his recent monograph give supplementary new data.

It is the purpose of this article to present a condensation of Meerson's work, w th

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reproduction of some of the original data within the limited scope of this article. The selection is arbitrary but it is hoped that it will give some of the essential results which otherwise would not be easily available to Western cardiologists.

Meerson's large experimental material (about 500 rabbits and 50 dogs) is subdivided into smaller subgroups for the different phases of compensation-decompensation and different types of analysis. Controlled aortic stenosis was produced narrowing the lumen to rather precisely one fourth or one third of its original size. Three phases are separated: for several days after the operation there was acute decompensation (phase 1) from which the majority (80 per cent) of the animals recovered; in the surviving animals the compensatory phase (phase 2) developed lasting for many months, and was followed by the final decompensation (phase 3).

There are drastic changes in the acute phase of decompensation. The heart weight increases by about 80 per cent within 5 days associated with pulmonary congestion, hydrothorax, ascites, T wave inversion, Q-T prolongation, swelling and separation of fibers in the myocardium, and degenerative changes of cardiac nerve endings (edema of neurons, vacuolization of the protoplasm). There is a profound drop in glycogen and creatine phosphate (Figs. 1 and 2) associated with a relatively small increase in lactate, whereas ATP does not change. Because of hydration of the myocardium its protein content decreases, more so in the myofibrils (T fraction by 35 per cent of the initial value) than in the sarcoplasm (12 per cent). ATPase activity† is increased, which may be interpreted as an emergency enzyme reaction.

The pronounced increase in heart weight during the first 5 days after operation is only in part due to hydration since the dry substance decreases only by 14 per cent according to Table 5 in Meerson's first monograph[5] i.e., from a control value of 18.6 per cent to 15.9 per cent. After 2 weeks, the dry substance is slightly above the initial value (20.27 per cent) and remains constant at that level (20.0 per cent after 30 days to 18 months). The initial drop and later increase in the dry substance in reference to the control level are statistically highly significant.

After the rapid increase in the first 5 days the heart weight remains constant for about 1 month although the initial hydration has disappeared and therefore shows ventricular hypertrophy. The heart weight increases slowly after 1 month (without change in hydration) up to twice the original weight at the end of the third month after experimental aortic stenosis. However, in Meerson's experiments the thickness of the ventricular wall did not change so that the increased heart weight is in proportion to the increased heart size (diastolic volume). This is an important difference from human left ventricular hypertrophy in aortic stenosis.

In the acute phase of decompensation DNA (deoxyribonucleic acid) decreases and RNA (ribonucleic acid) increases. In the compensatory phase (3 months) DNA drops further from the initial level and this decrease continues during final decompensation (6 months). RNA drops slowly to its initial level but the ratio RNA/DNA increases from 3.7 (control value) to 4.5, 5.6 and 12.8 at 1 week, 3 months and 6 months after experimental aortic stenosis, respectively. Most interesting is the increased absorption of

Table I. Mean number of counts per minute per 10 mg. protein in rabbits before and after experimental aortic stenosis

Time	Number of rabbits	Heart	Plasma
Control	4	126	109
After stenosis			
2 days	4	232	158
7 days	4	239	298
30 days	4	150	—
155 days	4	71	199

The protein fractions were determined by the method of Ivanov and associates. The T fraction, measured by means of electrophoresis, consists of tropomyosin and ... type of protein recently described by several authors.[9-12]

†ATPase activity was determined by the method of Zubenko.[13] Inorganic P resulting from hydrolysis of ATP is determined by means of Lowry and Lopez method (Journal of Biological Chemistry 162:421, 1946). The difference in inorganic P before and after hydrolysis (per gram of fresh myocardial tissue) serves as criterion of ATPase activity.

Table I

Case	Age Sex	Height	Body build	Diagnosis	Preformula weight (lb.)	Postformula		Digitalis	Diuretics
						Weight (lb.)	Days		
1	72 M	5 11	L	A.S.H.D. congestive failure, diabetes mellitus, obesity, gout	215½	202¾ 198¼ 187½	2 4 50	P	P
2.	83 M	6	L	A.S.H.D. recent myocardial infarction, congestive failure, obesity	216¼	203½ 198½ 193½	7 22 48	P	P
3	53 M	5 11½	L	H.H.D. congestive failure, osteoarthritis, obesity	249	236 234½ 222¾ 210 200½	5 13 40 74 102	0	M(×1)
4.	69 M	6	L	A.S.H.D. recent myocardial infarction, congestive failure, obesity	207½	201¾ 193½ 191	4 19 49	0	P
5	78 F	5 4	M	H.H.D. and A.S.H.D. recurrent congestive failure, diabetes mellitus	138	134¼ 131¼	1 10	P	P M(×1)
6.	65 F	5 4	M	A.S.H.D. previous myocardial infarction, acute pulmonary edema	132	125	3	P	C M(×1)
7	59 M	5'8	L	R.H.D. aortic stenosis, mitral insufficiency, coronary insufficiency, congestive failure, obesity, diabetes mellitus, subsequent myocardial infarction	213	209¼ 206	7 15	0	M(×1)
8.	76. F	5 3	M	A.S.H.D. auricular fibrillation, left bundle branch block, congestive failure	(1)132 (2)134 (3)145	129½ 128¾ 131 136 131 125	2 6 4 1 2 15	P P P	P M(×1) P M(×1)

*Including subsequent hypocaloric or sodium-poor diet.
A.S.H.D. Arteriosclerotic heart disease. H.H.D. Hypertensive heart disease. R.H.D. Rheumatic heart disease. S: Small frame. ... concomitant oral diuretics with formula. M(×1): One mercurial injection with formula. (Table I is continued on page 35.)

A number of these patients had been taking oral diuretic agents at the time their congestive failure recurred. In most instances the dose was increased. A single injection of a mercurial diuretic was administered initially to the majority of patients when they presented with moderate or advanced congestive failure. On the other hand, a marked diuresis was achieved in several edematous patients in whom diuretics and spironolactone were purposely withheld.

Sedation and other supportive measures were prescribed as indicated. Previous

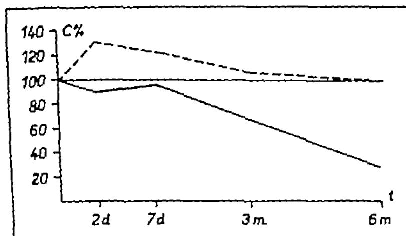


Fig 1 Relative changes in RNA (*dashed line*) and DNA (*solid line*), in per cent of normal control t = time after experimental aortic stenosis, d = days, m = months. (From Meerson, F Z. On the Mechanism of Compensatory Hyperfunction and Insufficiency of the Heart, Cor et Vasa 3(3):161 1961 Figure 5 p 165)

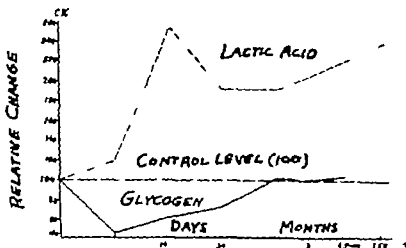


Fig 2 Relative changes in lactate (*dashed line*) and glycogen (*solid line*), in the left ventricle of rabbit after experimental aortic stenosis over a period of 1½ years (From Meerson, Figure 41 p 135)

labeled methionine S^{35} in the phase of acute decompensation [42] Methionine S^{35} (6 000 impulses per minute per 1 gram of body weight) was administered to rabbits 18 hours after the last intake of food The animals were sacrificed 4 hours later and the radioactivity in the dry protein of the heart was measured. Table I shows the results of this series.

The increased uptake of S^{35} is interpreted as increased protein resynthesis.

It is implied that the increased protein synthesis is associated with a rapid increase in heart weight, and it may be consistent with this interpretation that the protein synthesis at the time of fully developed hypertrophy as investigated by means of the uptake of S^{35} decreases to the normal level, and below the normal level in the final decompensatory phase Degenerative histologic changes are present in the myocardium at the time of increased

uptake of S^{35} whereas in the later phase of compensatory hypertrophy and decrease in the uptake of S^{35} to the original level enlargement of the diameter of myocardial fibers with increased size of their nuclei was found histologically. However, it is known that in ventricular hypertrophy the nuclei increase proportionally much less than the myofibrils. The functional significance of the increased S^{35} in the early phase of acute decompensation needs still further exploration. Meerson[19] believes that the increased protein synthesis is the main feature responsible for the increase in heart weight in the first week. In recent experiments with labeled C^{14} glycine in rats with experimental aortic coarctation an increase in the uptake of C^{14} similar to the increase in the uptake of S^{35} in experimental aortic stenosis was obtained. It is difficult, however, to estimate the increase in heart weight from the increased uptake of S^{35}. The maximum storage of S^{35} occurs on the second day, at the time when, according to histologic investigations by Meerson, there is most likely an increase in the extracellular space, although it was not directly determined. The fast initial increase in the heart weight attains the maximum at the fifth to seventh days.

In view of the increased protein resynthesis in the myocardium during the postoperative decompensation and early compensatory hypertrophy, the changes in *free amino acids are of interest (Table II)*. The changes in the various free amino acids are quite different. In the phase of acute decompensation there is a pronounced drop in glutamine, theonine, and alanine content; these return to or exceed the initial values during compensation. Tyrosine and phenylalanine are markedly increased.

The pattern of changes suggests that the new proteins synthesized are different from, or in a different proportion than, the normal proteins, and, in this connection, the continuous drop in DNA is of interest. Perhaps this may be of consequence for the ultimately developing decompensation.

In the latest series[*] acute experimental aortic stenosis was studied in greater detail in 22 dogs. The aortic lumen was constricted in six consecutive steps with 10-minute intervals from 80 to 50, 50, 40, 30, 20, and 10 per cent of the initial lumen. In the last step, with a lumen of only 10 per cent of the original size, the coronary flow and oxygen consumption per 100 grams of left ventricular musculature per minute increases about three times ($p \leq 0.001$) in confirmation of known information. The blood pressure was continuously recorded in both auricles and ventricles and in the aorta, the left ventricular circumference was determined by a modification of Rushmer's method,[*] and the left ventricular diameter was ascertained by means of V. C. Siniakov's ultrasonic method.

Table III shows a summary of the results. The (expected) increase in left ventricular systolic pressure and decrease in aortic systolic pressure with increasing stenosis is paralleled by the increase in total left ventricular work (involving left ventricular pressure) and decrease in external work (as defined by Meerson, involving aortic pressure). Of particular interest is the decrease in the peripheral vascular resistance (PVR), which is a true compensatory reaction that decreases the left ventricular overload. Since the aortic pressure beyond the point of stenosis is decreased, the decrease in PVR cannot be mediated by aortic or carotid baroreceptors. Meerson holds that it must be mediated by receptors in the left ventricular wall, and he gives several examples from clinical experience to support his view that this compensatory reaction occurs also in man and has considerable clinical importance. This was experimentally demonstrated with two typical examples (Meerson, Fig. 10). In one dog with good tolerance (compensation) to experimental aortic stenosis the cardiac minute volume was well maintained at the control level (before stenosis), whereas the peripheral vascular

Amino acids were determined by the method of Gara (no reference given) by means of photoelectric colorimetry in 4 c.c. $CuSO_4$ solution in 75 per cent alcohol.

*No literature reference to Rushmer's method is given, but the main features are described. Small discs of barium titanate (6 mm. in diameter) sewed on the anterior and posterior walls of the left ventricle serve as electrodes. The ultrasonic frequency used is 1,000 kilocycles. The calibration is based on the speed of the ultrasonic signals. Rectangular impulses of 2.5 sigma are used.

resistance dropped to 10 per cent of the initial level In the other dog with poor tolerance the peripheral vascular resistance *increased* whereas the cardiac minute volume decreased about 50 per cent.

In the second phase of relatively constant hyperfunction the symptoms of cardiac decompensation (pulmonary congestion edema) T wave inversion and most of the degenerative changes of muscle fibers and nerve endings disappear Only a small fraction of the nerve endings degenerate irreversibly However the increased pressure in the left ventricle (about 300 mm Hg) is maintained and left ventricular hypertrophy develops (characterized mainly by an increase in the thickness and length of myocardial fibers rather than by an increase in their number as has been known for some time)

The time-course of heart weight and some of the biochemical changes in the

Table II Free amino acids (mg./100 gram fresh weight) in the left ventricle of rabbits before and after experimental aortic stenosis

Amino acid	*Control*	*After operation*			
		2 days	*7 days*	*1 mo.*	*5 mo*
Lysine	10 3	10 3	12 0	12 0	16 4
Asparagine	7 1	5 1	5 7	7 1	6 9
Glutamine	27 9	12 1	14 0	21 4	25 9
Theonine	5 9	1 2	3 0	5 9	6 2
Alanine	17 1	5 5	10 1	17 1	19 8
Tyrosine	7 7	31 0	22 0	23 3	29 2
Valine	3 6	—	—	5 0	4 9
Phenylalanine	7 8	18 0	—	16 6	23 4

Table III Systolic pressure in left ventricle and aorta pressure gradient cardiac minute volume (ml./min.) peripheral vascular resistance (PVR) absolute (dynes sec cm⁻⁵) and relative (per cent of initial value) left ventricular work in progressive experimental aortic stenosis Means of 2 dogs

	Narrowing of the aortic lumen per cent of initial value (0)							*Release of aortic stenosis*
	0	*20-50*	*50-60*	*60-70*	*70-80*	*80-90*	*90-95*	
PVR (absolute)	2 022	1 761	1 865	1 780	1 303	1 115	474	3 624
PVR (relative)	100	87	92	88	64	55	23	179
Mean systolic pressure								
Left ventricle (mm. Hg)	122	126	129	151	157	174	247	117
Aorta (mm. Hg)	104	99	94	93	79	58	47	86
Ventricular aortic gradient	18	27	35	58	78	116	200	31
Cardiac minute volume (ml.)	4 106	3 934	3 936	3 692	3 374	3 970	3 296	3 345
External left ventricular work* (kg./min.)	5 3	5 1	5 3	4 4	3 1	3 6	2 2	3.8
Total left ventricular work†	5 9	6 1	6.4	6.8	6 0	8 3	8.9	4.3

*Mean systolic pressure in aorta × stroke volume + $\frac{Mv^2}{2g}$ (M = weight of stroke volume; v = flow velocity in aorta [illegible]).

†Mean systolic pressure in left ventricle × stroke volume [illegible]

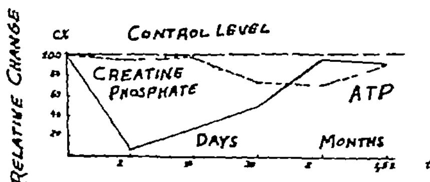


Fig. 3. Creatine phosphate (*solid line*) and ATP (*dashed line*), in per cent of normal control level, in the left ventricle of rabbits after experimental aortic stenosis over a period of 1½ years. (From Meerson, Figure 42, p. 135.)

m ocardium are shown in Figs. 1 to 3 and Tables I to III. After the initial drop the phosphocreatine and glycogen content increase during the compensatory phase to reach the initial (control) level. The lactate rises during the first 2 weeks and remains elevated, which according to Meerson is suggestive of myocardial hypoxia probably due to the failure of capillaries to grow with the increasing ventricular mass. Later progressive secondary fibrosis develops which is one of the main factors contributing to the development of final decompensation. Meerson found degenerative changes to be most marked in the central zone of muscle fibers, i.e., in the area of nuclei. The fraction T (after an initial drop of 35 per cent) and ATPase activity reach a peak of 160 to 170 per cent of the initial level 1.5 months after the experimental aortic stenosis, from which peak the ATPase declines gradually to the control level and fraction T to 25 per cent below the control level. DNA drops steadily from the seventh postoperative day to 30 per cent of the initial level 6 months later. The increase in ATPase during the compensatory phase is interpreted by Meerson as improved capacity of the myosin for dephosphorylation of ATP and utilization of energy for muscular contraction. The peak of ATPase activity coincides with the optimum compensation and is considered to be one of the principal compensatory factors. By the same token the decrease in ATPase after the forty

Table IV. *Changes in the phase of acute decompensation and compensatory hyperfunction*

	Acute decompensation	*Relatively stable compensatory hyperfunction*
Heart weight	Increased 30-50%	Increased 95-100% stable
Diameter of muscle fiber	Increased 30-50%	Increased 95-100% stable
Sarcoplasm	Light color little eosin absorption	Dark color pronounced eosin absorption
Nuclei	Light color irregularly enlarged	Hyperchrome enlarged
Myofibrils	Separated	Compact
Cardiofibrosis	Absent	Beginning
Glycogen	Pronounced decrease	Normal
Lactat	Increased (20%)	Greatly increased (200-300 per cent)
Phosphocreatine	Decreased (to 10% of control level)	Normal
ATP	Normal	Normal
ADP	Normal	Normal
Protein synthesis	Increased 100 per cent	Normal
RNA	Increased	Normal
DNA	Normal	Decreased
Dry substance	Decreased 15 per cent	Normal

fifth day shows approaching failure of energy utilization. Thus, biochemical changes precede the development of the final decompensation and electrocardiographic changes (left ventricular strain pattern). This corroborates findings by Rabkina [41] who found in 15 rabbits with ventricular hypertrophy produced by experimental arterial hypertension a drop in glycogen and phosphocreatine of 37 and 59 per cent respectively as compared with 15 controls. There was no significant change in ATP or dry substance. The biochemical changes, which are quite similar to the changes in left ventricular hypertrophy about 1 month after experimental aortic stenosis in Meerson's experiments, preceded the development of left ventricular strain pattern in the electrocardiogram.

In view of the change in hydration it is regrettable that some of the biochemical concentrations are expressed per gram of dry weight and others per gram of fresh (wet) weight. A uniform reference would be preferable, but the changes in the concentrations of most of the various substances analyzed cannot be explained by changing hydration.

Meerson summarizes the changes in the phase of acute decompensation and compensatory hyperfunction as shown in Table IV.

The functional range of changes in the heart rate was investigated by the reaction to nitroglycerin (producing an increase) and to the breathing of NH fumes (producing a reflex bradycardia). The range is expressed as the difference between fastest and slowest heart rates under these conditions. In normal rabbits this difference is from 230 to 270 beats per minute (mean 255). It decreases considerably during the acute decompensation (mainly because of less pronounced reflex bradycardia) and it remains decreased during the phase of compensation (mean 200). With the onset of final decompensation the difference decreases sharply to 150 and continues to decrease until death (to about 40). The narrowing of the range of heart rate shows a decrease in functional adaptability and may be of potential interest for clinical exploration in man (although a different stimulus particularly for the reactive bradycardia, is advisable). It is quite possible that the degeneration of cardiac nerve endings* is involved in the narrowing of the range of functional adaptability. Parallel with the decrease in functional adaptability is the decrease in cardiac reserve, due to the continuous overload of the left ventricle which involves in the phase of compensatory hypertrophy nearly the whole contractile capacity even in the resting condition.

Of great interest is the abrupt decrease in unconditioned and conditioned reflexes (reflex apnea and bradycardia) during the acute phase of decompensation in the first days after experimental aortic stenosis. Fig. 4 shows in two representative examples the drop in the conditioned apnea (in per cent of normal response) and in the unconditioned apnea (in seconds) produced by the breathing of NH fumes. There is in contrast to the recovery of hemodynamic functions and chemical changes no recovery of reflexes in the phase of compensatory hyperfunction. It is quite possible that this may be due to secondary cerebral ischemia, and in this connection it may be mentioned that Enzer, Simonson and Blankstein found a decrease in the fusion frequency of flicker in patients with cardiac decompensation.

The amplitudes of the electroencephalogram (premotor and visual zones) are drastically decreased during the phase of acute decompensation (Fig. 5) but recover within 2 weeks. It is possible that conditioned reflexes are a more sensitive index of the functional state of the cerebral cortex than is the electroencephalogram.

For further exploration of the role of the cerebral cortex in cardiac decompensation the major part of the cerebral cortex was removed in 22 rabbits 20 days prior to the experimental aortic stenosis. Already 9 to 19 days after the aortic stenosis the T wave in Lead I became inverted and micronecrosis was found in the myocardium in part of this group much earlier than usual. However *in over half of the animals* with removed cerebral cortex the development of compensatory hyperfunction was

*Recently, Meerson[?] found ATPase activity per milligram of m[illegible] in control animals to be 2.8 [illegible] days, 45 days, and 90 days after experimental aortic stenosis it was 3.11, 4.06, and 2. respectively, which shows the terminal drop more distinctly.

Table V. Effect of therapy (administration of B_{12}, ATP, and methionine) in the late phase of experimental aortic stenosis in rabbits on ATPase, DNA, and RNA in left ventricle

	ATPase (mg./1 Gm. fresh tissue)	DNA (gamma/1 Gm. fresh tissue)	RNA (gamma/1 Gm. fresh tissue)
Group I Normal control	18 03 ± 813	763 ± 16 2	2 700 ± 112 4
Group II Aortic stenosis	9 34 ± 1 984	249 ± 23 9	2 410 ± 195
Group III Aortic stenosis plus therapy	34 46 ± 1 465	454 ± 11 9	1 265 ± 57 3
Δ I II	−8 69**	−324	−190
Δ II III	+25 11**	+205	−1 535

**p ≤ .01

quite similar to that in the animals with intact cerebral cortex. It appears that compensatory processes are maintained after removal of the cerebral cortex, but there is some impairment in a substantial percentage of the animals. The groups are too small for any precise statistical prediction, but the results are of potential clinical interest. Although the interference of experimental aortic stenosis, even in the phase of compensation, with cerebral function (as shown by conditioned reflexes) appears to be well established, the important question of a possible vicious circle (interference of impaired cerebral function with cardiac compensation) deserves further exploration.

Meerson summarizes his conclusion as follows: "As a result of prolonged and relative stable compensatory cardiac hyperfunction, a chain of biochemical changes develops leading to a more or less pronounced loss of contractile capacity of actomyosin. These changes are for a long time only preliminary to the development of decompensation. They become more pronounced with the disturbance of neurohormonal cardiac regulations and structural damage to the myocardium; finally, with the continuing overload (disproportion between contractile capacity and functional demand) they lead to the development of the complex cardiac decompensation." Thus cardiac compensation and decompensation are viewed as a complex phenomenon involving multiple vicious circles.

In his latest publication, Meerson draws attention to the similarity between changes in the relative compensatory phase and senile myocardial changes. In both conditions, there is hypertrophy of myocardial fibers (although not necessarily of the whole heart in senility), myocardial fibrosis, decrease in protein synthesis (tagged amino acid absorption), decrease in DNA, increase in the ratio RNA/DNA, decrease in oxidative phosphorylation, and decrease in the range of functional adaption of the heart rate.

Since Meerson believes that the decrease in the ATPase activity of myosin is one of the most important features in the chain leading to cardiac decompensation, he assumes that donors of SH groups (such as cysteine, methionine) may counteract this process. It is of great interest that systematic administration of vitamin B_{12}, ATP (intramuscular), and methionine (oral) reversed some of the changes in the late phase of developing decompensation in experimental aortic stenosis in rabbits (Table V).

Most striking was the effect on DNA. In experimental animals it drops 6 months after aortic stenosis to 215 gamma per 1 Gm. fresh weight from the initial (control) value of 763 ±16 2. In the treated animals with aortic stenosis, DNA increased to 454 ± 11 9, and the difference between treated and untreated animals was statistically highly significant (p≤ .001). The treatment increased significantly the ATPase activity (Table V). Of course, it cannot be expected that this treatment would be effective in senile myocardial changes, but the results may suggest new approaches to the treatment of cardiac decompensation.

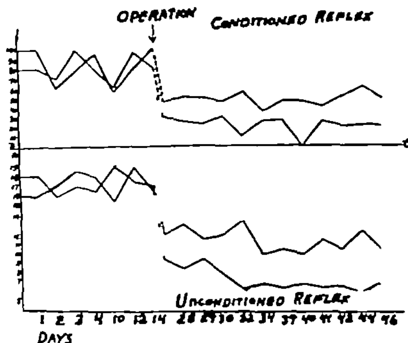


Fig. 4. Changes in conditioned reflexes (*upper part*, conditioned apnea, in per cent of control period before operation) and unconditioned reflexes (*lower part*, apnea in seconds), in 2 rabbits before and after experimental aortic stenosis. (From Meerson, Figure 57, p. 226.)

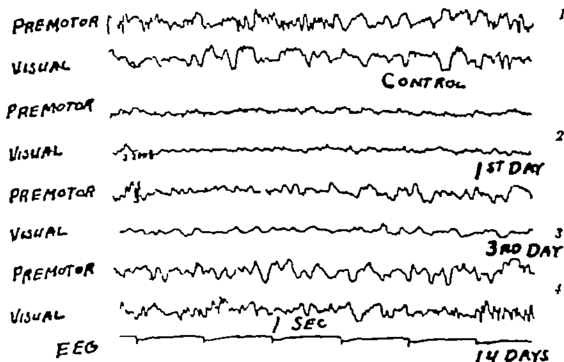


Fig. 5. Typical changes in the electroencephalogram of the premotor and visual zones in a rabbit before (*control*), 2 days, 3 days and 14 days after experimental aortic stenosis. (From Meerson, Figure 58, p. 227.)

Meerson's discussions in his publications particularly in his two monographs are thoughtful and stimulating but in view of the limited scope of this review we concentrated mainly on some of the actual experimental data. Even though Meerson's studies are quite comprehensive some additional information is desirable such as electrolyte (particularly potassium) changes general acidosis blood lactate pCO_2 arterial O saturation plasma methionine levels heart levels of hydroxyproline or other amino acids related to connective tissue in the phase of decompensation and their relationship to the changes in the heart. Of course the successful completion of even a large set of experimental data always poses many additional problems.

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Fundamentals of clinical cardiology

Basal diastolic murmurs

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With the development of cardiac surgery it has become increasingly apparent that an accurate preoperative diagnosis of cardiac lesions is essential if optimum surgical results are to follow. This awareness has stimulated a renewed interest in the study of heart sounds and murmurs, with the development of many new and objective methods to better evaluate them. As might be anticipated, these studies have changed a number of earlier clinical concepts in regard to the origin and significance of cardiac murmurs, and many details of cardiovascular sound which were previously considered to be of only academic interest are now of great practical diagnostic importance.

The purpose of this paper is to review the problem of basal diastolic murmurs that arise from incompetent semilunar valves, with particular reference to etiology, sound characteristics, diagnostic methods, and differential diagnosis. It should be realized that diastolic murmurs at the base of the heart may result from other than incompetent semilunar valves. For example, such murmurs may be heard in certain instances of patent ductus arteriosus, aortic-pulmonary septal defects, pulmonary arteriovenous fistulas, coronary arteriovenous fistulas (especially those communicating with the left ventricle), and pericarditis, among others. This discussion will deal only with the diastolic murmurs produced by regurgitation through incompetent aortic or pulmonary valves.

Etiology

Aortic regurgitation. A basal diastolic murmur that arises from an incompetent aortic valve is the result of aortic valve disease or deformity, or dilatation of the aortic valve ring. As can be seen from Table I, the specific etiologies are many and may be congenital, acquired, or functional.

Aortic regurgitation occasionally occurs as an isolated congenital anomaly, but more commonly it is associated with other congenital or hereditary cardiac defects. As an isolated lesion, a bicuspid aortic valve may become incompetent because of improper coaptation of the two valve leaflets or as a result of bacterial endocarditis, which has a high predilection for involving the bicuspid valve. More often the aortic regurgitation is the result of secondary valvular sclerotic changes and the hypertension of aortic coarctation with which the bicuspid valve is so frequently associated.

Marfan's syndrome and idiopathic cystic medionecrosis of the aorta are rare heritable diseases which frequently involve the ascending aorta, aortic valve ring, and sinuses and occasionally the aortic valve cusps, producing aortic regurgitation. The majority of patients with Marfan's syn

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Table I. Causes of aortic valve incompetence

I. Congenital
  1. Isolated aortic regurgitation
  2. Bicuspid aortic valve
  3. Coarctation of the aorta
  4. Marfan syndrome
  5. Idiopathic cystic medionecrosis
  6. Aortic stenosis: supravalvular, valvular, subvalvular
  7. Ventricular septal defect with aortic insufficiency
II. Acquired
  1. Rheumatic heart disease
  2. Syphilitic aortitis
  3. Dissecting aneurysm of the aorta
  4. Rheumatoid spondylitis
  5. Bacterial endocarditis
  6. Systemic lupus erythematosus
  7. Traumatic aortic insufficiency
  8. Aortitis of undetermined etiology
III. Other causes
  1. Aneurysms of the sinuses of Valsalva
  2. Fenestrations of aortic valve
  3. Hypertension

drome and aortic regurgitation have characteristic features which are easily recognized. Some, for example, the *formes frustes*, do not exhibit the usual manifestations and the diagnosis in these cases can be established by aortography or aortic valvulography that demonstrates marked localized dilatation of the ascending aorta with or without enlarged cusps or aortic sinus aneurysms. We have established the diagnosis in 3 such patients utilizing aortic valvulography during the past 3 years.

Congenital aortic stenosis, whether supravalvular, valvular, or subvavular, is frequently associated with variable degrees of aortic regurgitation. We have studied 5 patients with supravalvular aortic stenosis and 2 had aortic regurgitation demonstrable by angiographic techniques. The incidence of aortic regurgitation with the valvular and subvalvular forms is said to approximate 30 to 40 per cent.[4] Utilizing aortic valvulography, we have found the frequency to be even greater.

The syndrome of ventricular septal defect with aortic regurgitation has been reported with increasing frequency in recent years. The ventricular septal defect is usually small or moderate in size and is associated with prolapse of the right or posterior aortic valve cusp adjacent to the defect.[4] The preoperative diagnosis of this syndrome is particularly important since it may be confused with patent ductus arteriosus, ventricular septal defect with pulmonary hypertension and relative pulmonic insufficiency, aortic-pulmonary septal defect, or ruptured aneurysm of the sinuses of Valsalva.

The most common cause of aortic regurgitation is *acquired* heart disease, either rheumatic or syphilitic. As might be expected, aortic regurgitation in patients below the age of 40 is most likely rheumatic. The results of recent objective studies[3,4] indicate that the actual incidence of aortic regurgitation in rheumatic heart disease is even greater than was previously thought by clinical evaluation alone. Utilizing aortic valvulography, we have demonstrated a degree of aortic regurgitation in the great majority of patients who were considered clinically to have a Graham Steell murmur of relative pulmonic insufficiency. We now consider that until proved otherwise all basal diastolic murmurs in patients with rheumatic heart disease represent aortic regurgitation.

Aortic regurgitation as a result of syphilis is secondary to the aortitis and dilatation of the aorta rather than to intrinsic valvular changes. The dilated aorta causes a stretching of the normally redundant leaflets and a separation of the commissures with resultant regurgitation. There may be certain intrinsic valvular changes associated with this, such as rolling of the free edges or eversion of the cusps, but these are probably secondary to the mechanical effects of the regurgitating stream of blood.[3]

Dissecting aneurysm of the ascending aorta is frequently associated with the murmur of aortic regurgitation. In fact, the onset of a basal diastolic murmur in a patient with chest pain affords an important clue that dissection may have occurred. The aortic regurgitation may result from distortion of the aortic valve ring or cusps by a medial hematoma or may be due to actual detachment of an aortic valve cusp. In other instances the murmur may antedate dissection and be related to an underlying disease, i.e.,

Spironolactone	*Adrenocortical steroids*	*Clinical features*
0	0	See text
0	0	
0	0	Prompt response of classic congestive failure to formula and oral digitalization. Diuretics withheld because of patient's large prostate and possible distention of bladder. Prompt improvement in ability to void after daily intravenous estrogens (Premarin Intravenous) when patient declined catheterization. Subsequent oral diuretics (benzthiazide) taken without difficulty. Able to return to his job as insurance executive for 4 months (as of this report)
0	0	Had previously lost weight from 176¾ to 152 pounds, on formula 1 year prior to the onset of congestive failure. Cholesterol at that time had decreased from 429 to 284 mg. per cent over 2 month period. Prompt clinical response—including relief of angina pectoris—followed diuresis with formula, digitalis, and oral benzthiazide. With use of formula for lunch, weight declined to 149¾ pounds 2 months later
0	0	Previous angina pectoris, dyspnea on slight exertion, and intermittent claudication had responded dramatically to loss of weight from 215¾ to 186¼ pounds—largely by means of formula. Digitalis withheld at that time, but kept on maintenance oral diuretic therapy. Classic congestive failure recurred 4 months later. Gratifying and dramatic disappearance of her dyspnea, wheezing, and angina shortly after diuresis and restoration of myocardial competency
P	0	Weight had stabilized at 207 pounds on digitalis, hydrochlorothiazide, mercurial injections, and spironolactone (100 mg. four times daily) without regression of congestive failure. Diabetic glucose tolerance curve and rise in serum sodium associated with glucose loading. Diuresis followed formula—even with cessation of spironolactone and oral diuretic. Subsequent standard low-sodium diet
0	0	Recurrent congestive failure over 18 months. Dry weight of 130 pounds finally maintained with benzthiazide (50 mg. twice a day) and parenteral mercurial diuretic every 10 days. Dramatic improvement of last bout of classic failure by formula without resort to spironolactone. Interval feedings prevented his "weakness and nervousness" (attributed to hypoglycemia)

In at least 4 patients in whom its use was being contemplated after previous digitalization, diuretic therapy, and even adrenocortical steroid therapy had failed to check the progression of congestive failure, spironolactone therapy was obviated by a prompt diuresis on formula. The use of formula proved successful in 2 patients (Cases 12 and 20) after these measures plus spironolactone were ineffective. The anasarca in Case 20—an obese and diabetic woman in congestive failure—failed to respond to a standard 1.0 Gm. sodium diet, even while she was on digitalis, complete bed rest in a hospital, hydrochlorothiazide (50 mg. twice a day), spironolactone (100 mg. four times a day), and parenteral mercurial diuretics. On this program her weight had remained at 207 pounds for several days until formula was instituted. Spironolactone could be completely stopped and the hydrochlorothiazide was briefly discontinued. Within 13 days her weight decreased to 193½ pounds, with a gratifying loss of her marked peripheral edema. A standard low-sodium diet was then resumed.

The combined use of formula and spironolactone achieved a dramatic and sustained diuresis in 2 patients. Hospitaliza

Marfan's syndrome, hypertension, coarctation, or aortic cystic medionecrosis.[1]

Aortic regurgitation also occurs in males with rheumatoid spondylitis. The pathologic picture is one of thickened, deformed aortic valve leaflets with rolled edges. There may be some dilatation of the aortic valve ring and aorta but rarely is there the degree of separation of the cusps that occurs with syphilitic aortitis. This lesion is becoming recognized more frequently and has been estimated to occur in approximately 2 per cent of the patients with ankylosing spondylitis.

Another important and not infrequent cause of acquired aortic regurgitation is bacterial endocarditis, which usually affects valves previously damaged by rheumatic fever. Trauma, systemic lupus erythematosus,[9] and aortitis of undetermined etiology[11] are much rarer causes of acquired aortic valve incompetence.

We have listed aortic sinus aneurysms under "other causes" of aortic regurgitation since these lesions may be congenital, either isolated or associated with Marfan's syndrome and cystic medionecrosis of the aorta, or they may be acquired secondary to syphilis or bacterial endocarditis. The right coronary sinus is by far the one most commonly involved. Prior to rupture, a basal diastolic murmur of aortic regurgitation is frequently heard. After rupture of the aneurysm, usually into the right atrium or ventricle, a continuous murmur develops. If, however, the lesion is associated with pulmonary hypertension, or, more rarely, if the aneurysm ruptures into the left ventricle, the murmur may be to and fro in character.

Fenestration of the aortic valve cusps is a common autopsy finding and can be demonstrated in as high as 70 to 80 per cent of routine postmortem examinations.[12] Although this lesion only rarely results in the murmur of aortic regurgitation and is even less frequently significant hemodynamically, it must be considered in the differential diagnosis of basal diastolic murmurs.

Functional aortic regurgitation is present in 5 to 10 per cent of the patients with significant systemic hypertension, but the murmur bears no consistent relationship to the manometric level or duration of the hypertension.[13,14] A decrease in or disappearance of the murmur as blood pressure decreases lends support to the view that this murmur is functional in origin. Functional basal diastolic murmurs that generally are considered to be aortic in origin have also been reported in patients with severe anemia and congestive heart failure. The nature and exact origin of these functional murmurs, however, have not been clarified by objective studies.

Pulmonic regurgitation. Although there are many causes of pulmonary valve incompetence (Table II), its incidence is distinctly less than that of aortic regurgitation. The true incidence of pulmonic regurgitation is difficult to assess, however, since most of the available statistics have not been accompanied by adequate supporting evidence.

Congenital malformation of the pulmonary valve, either isolated or associated with other cardiac defects, is a rare cause of organic pulmonic regurgitation. In 1,000 cases of congenital heart disease studied by Abbott,[15] there were only 21

Table II. Causes of pulmonary valve incompetence

I. Organic pulmonic regurgitation
  A. Congenital
    1. Deformed or absent valve
    2. Bicuspid valve
    3. Supernumerary cusps
    4. Associated with pulmonic stenosis
  B. Acquired
    1. Bacterial endocarditis
    2. Rheumatic heart disease
    3. Syphilis
    4. Fenestrations of pulmonary valve cusps
    5. Pulmonary valve surgery
    6. Carcinoid
    7. Trauma
    8. Pulmonary artery aneurysms
II. Functional pulmonic regurgitation
  A. Congenital
    1. Primary pulmonary hypertension
    2. Secondary pulmonary hypertension (Eisenmenger physiology)
    3. Idiopathic dilatation of the pulmonary artery
  B. Acquired (pulmonary hypertension)
    1. Mitral stenosis
    2. Bronchopulmonary disease
    3. Pulmonary emboli and thrombi
    4. Chronic left ventricular failure

Table I. Causes of aortic valve incompetence

I. Congenital
  1. Isolated aortic regurgitation
  2. Bicuspid aortic valve
  3. Coarctation of the aorta
  4. Marfan syndrome
  5. Idiopathic cystic medionecrosis
  6. Aortic stenosis, supravalvular, valvular, subvalvular
  7. Ventricular septal defect with aortic insufficiency

II. Acquired
  1. Rheumatic heart disease
  2. Syphilitic aortitis
  3. Dissecting aneurysm of the aorta
  4. Rheumatoid spondylitis
  5. Bacterial endocarditis
  6. Systemic lupus erythematosus
  7. Traumatic aortic insufficiency
  8. Aortitis of undetermined etiology

III. Other causes
  1. Aneurysms of the sinuses of Valsalva
  2. Fenestrations of aortic valve
  3. Hypertension

drome and aortic regurgitation have characteristic features which are easily recognized. Some, for example, the *formes frustes*, do not exhibit the usual manifestations, and the diagnosis in these cases can be established by aortography or aortic valvulography that demonstrates marked localized dilatation of the ascending aorta with or without enlarged cusps or aortic sinus aneurysms. We have established the diagnosis in 3 such patients utilizing aortic valvulography during the past 3 years.

Congenital aortic stenosis, whether supravalvular, valvular, or subvavular, is frequently associated with variable degrees of aortic regurgitation. We have studied 5 patients with supravalvular aortic stenosis, and 2 had aortic regurgitation demonstrable by angiographic techniques. The incidence of aortic regurgitation with the valvular and subvalvular forms is said to approximate 30 to 40 per cent.[3] Utilizing aortic valvulography, we have found the frequency to be even greater.

The syndrome of ventricular septal defect with aortic regurgitation has been reported with increasing frequency in recent years. The ventricular septal defect is usually small or moderate in size and is associated with prolapse of the right or posterior aortic valve cusp adjacent to the defect.[4] The preoperative diagnosis of this syndrome is particularly important since it may be confused with patent ductus arteriosus, ventricular septal defect with pulmonary hypertension and relative pulmonic insufficiency, aortic pulmonary septal defect, or ruptured aneurysm of the sinuses of Valsalva.

The most common cause of aortic regurgitation is *acquired* heart disease, either rheumatic or syphilitic. As might be expected, aortic regurgitation in patients below the age of 40 is most likely rheumatic. The results of recent objective studies[5,6] indicate that the actual incidence of aortic regurgitation in rheumatic heart disease is even greater than was previously thought by clinical evaluation alone. Utilizing aortic valvulography, we have demonstrated a degree of aortic regurgitation in the great majority of patients who were considered clinically to have a Graham Steell murmur of relative pulmonic insufficiency. We now consider that until proved otherwise all basal diastolic murmurs in patients with rheumatic heart disease represent aortic regurgitation.

Aortic regurgitation as a result of syphilis is secondary to the aortitis and dilatation of the aorta rather than to intrinsic valvular changes. The dilated aorta causes a stretching of the normally redundant leaflets and a separation of the commissures with resultant regurgitation. There may be certain intrinsic valvular changes associated with this, such as rolling of the free edges or eversion of the cusps, but these are probably secondary to the mechanical effects of the regurgitating stream of blood.[7]

Dissecting aneurysm of the ascending aorta is frequently associated with the murmur of aortic regurgitation. In fact, the onset of a basal diastolic murmur in a patient with chest pain affords an important clue that dissection may have occurred. The aortic regurgitation may result from distortion of the aortic valve ring or cusps by a medial hematoma or may be due to actual detachment of an aortic valve cusp. In other instances the murmur may antedate dissection and be related to an underlying disease, i.e.

characteristic feature is the basal diastolic murmur. Usually this is a high pitched blowing decrescendo murmur of low intensity which follows immediately the aortic component of the second heart sound and extends through variable lengths of diastole. Rarely there may be a gap between the second heart sound and the onset of the murmur or the murmur may be crescendo-decrescendo in character. Occasionally a loud musical "sea gull" regurgitant murmur may be heard with retroversion, perforation, or other deformity of an aortic cusp.

The characteristic diastolic murmur of aortic regurgitation, especially that of rheumatic heart disease, is best heard at Erb's point (the third left intercostal space adjacent to the sternum). We have been impressed by the frequency with which this murmur is heard only at this area in rheumatic aortic regurgitation of mild to moderate severity, as proved by aortic valvulography. This localization of the aortic regurgitant murmur causes considerable difficulty in differentiating it from the Graham Steell murmur of relative pulmonic regurgitation. The aortic diastolic murmur may also be heard at the second right intercostal space, and unless of low intensity, it is usually transmitted toward the apex. During this transmission the high-frequency components of the murmur are often attenuated so that it assumes a lower pitched rumbling character and may be confused with mitral stenosis. Occasionally, the diastolic murmur is heard best down the right sternal border when the aortic regurgitation is produced by syphilis, aortic cystic medionecrosis, aortic sinus aneurysm, or dissection of the aorta.[18]

The occurrence of an aortic systolic ejection murmur with uncomplicated aortic regurgitation is well recognized and results from an increased left ventricular stroke volume and flow velocity across a deformed valve without anatomic stenosis. A dilated ascending aorta may also contribute to the genesis of the murmur. The murmur may be quite loud and on occasion it may be accompanied by a thrill. On the other hand, the systolic murmur is often absent when the aortic regurgitation is not accompanied by left ventricular enlargement or an increase in the peripheral pulse pressure.

It should be emphasized that the intensity of the diastolic murmur of aortic regurgitation, like that of other murmurs, does not necessarily reflect its physiologic significance. This has become quite evident to us from the frequent disparity between the intensity of the murmur and the severity of the lesion as demonstrated by angiographic techniques.

Pulmonic regurgitation. The Graham Steell murmur of *functional* pulmonic regurgitation due to pulmonary hypertension has many of the characteristics of the murmur of aortic regurgitation. The large pressure gradient across the valve during diastole results in a high-velocity regurgitant flow and produces a high pitched, blowing decrescendo diastolic murmur. Usually it is of low intensity and short duration, but occasionally it may be quite loud (Grade 4 or 5/6) and long. Rarely, the murmur may be accompanied by a diastolic thrill. The murmur begins immediately after an accentuated pulmonic component of the second heart sound which is *not* widely split. The erroneous impression that the second sound in pulmonary hypertension is widely split probably arises from the misinterpretation of the opening snap of mitral stenosis as the pulmonic component of the second heart sound. The murmur is best heard at the third and fourth left intercostal spaces and is frequently transmitted down the left sternal border or toward the apex. It is rarely, if ever, heard at the right sternal border. A pulmonic systolic ejection click and systolic murmur frequently accompany the diastolic murmur.

The cardiovascular sound in *organic* pulmonic regurgitation is quite different from the Graham Steell murmur. In contrast to pulmonary hypertension, the diastolic pressure gradient across the pulmonic valve is small and results in a low velocity regurgitant flow and consequently a low pitched diastolic murmur. Characteristically, the murmur is harsher and crescendo-decrescendo in configuration and usually there is a short interval between the second heart sound and the onset of the murmur. A short pulmonic systolic murmur is invariably present, and the

pulmonic component of the second heart sound may be increased, decreased, or normal in intensity. Using intracardiac phonocardiography in 3 patients with organic pulmonic regurgitation, we found that the murmur recorded from the right ventricular outflow tract was identical in all respects with the murmur recorded from the chest.

Differential diagnosis

It is apparent that successful surgical correction of congenital or acquired heart disease depends on precise preoperative knowledge of both the anatomic site and severity of the lesions. Yet, all too frequently, there is a marked disparity between the preoperative clinical appraisal of the lesion and the findings revealed at the time of operation. The basal diastolic murmur has frequently been implicated in this regard, and the determination of the origin and significance of this murmur has provided one of the more difficult problems in contemporary cardiology.

Clinical appraisal of the murmur. Obviously, the correct clinical diagnosis in regard to the origin of a basal diastolic murmur is not always difficult to make. For example, the finding of a loud basal diastolic murmur at both the right and left sternal borders, in association with an aortic systolic murmur, a wide peripheral pulse pressure, left ventricular enlargement, and no evidence of pulmonary hypertension presents no problem in establishing the presence of aortic regurgitation. Likewise, the diagnosis of organic pulmonic regurgitation is apparent when one finds the characteristic low pitched crescendo-decrescendo basal diastolic murmur accompanied by vigorous pulsations of the pulmonary artery and no evidence of left ventricular enlargement or the peripheral signs of aortic regurgitation.

The difficult problem that arises is the differentiation of "adynamic" aortic regurgitation (i.e., without left ventricular enlargement or an increased peripheral pulse pressure) from relative pulmonic insufficiency associated with pulmonary hypertension. This differentiation may be extremely difficult and often impossible to achieve regardless of the clinical criteria used. The problem is particularly emphasized in patients with mitral stenosis and an associated basal diastolic murmur who are being considered for closed mitral commissurotomy. The basal diastolic murmur in these patients is often regarded as the Graham Steell murmur of relative pulmonic regurgitation if there is no left ventricular enlargement or peripheral manifestations of aortic regurgitation. This is especially so if there is clinical evidence of pulmonary hypertension as evidenced by an accentuated pulmonic second sound, an enlarged main pulmonary artery on fluoroscopy, and radiographic or electrocardiographic evidence of right ventricular enlargement. Other criteria to support the diagnosis of a Graham Steell murmur include localization of the murmur to the second and third left intercostal spaces, no evidence of aortic stenosis, and a small aorta on x-ray examination. On the basis of these clinical criteria, the reported incidence of relative pulmonic regurgitation in rheumatic heart disease is high, and has been estimated to occur in 10 to 15 per cent of the patients with mitral stenosis.[11] Unfortunately, the majority of reports have lacked objective supportive studies sufficient to substantiate the diagnosis.

To evaluate more objectively the basal diastolic murmur in these patients, we have used the technique of retrograde aortic valvulography for the detection of aortic regurgitation and have reported our earlier findings elsewhere. To date, we have now studied 33 patients with mitral stenosis in whom the diagnosis of a Graham Steell murmur would have been made by using the conventional criteria. None of these patients displayed peripheral manifestations of aortic insufficiency, and all had the clinical evidence of pulmonary hypertension as noted above. In no instance was left ventricular enlargement demonstrated by the electrocardiogram. In 7 patients, fluoroscopy provided evidence suggestive of left ventricular enlargement. It is extremely difficult, however, to evaluate left ventricular size radiographically when there is significant left atrial and right ventricular enlargement as seen in these patients. Moreover, mitral regurgitation was a complicating lesion in 6 of the 7 patients and could have

accounted for any possible left ventricular enlargement.

Of these 33 patients 24 were shown to have aortic regurgitation by aortic valvulography with graded severity ranging from 1 to 3+ (0 to 4+ scale). The clinical findings in the 9 patients *without* aortic regurgitation were similar in all respects to the findings in others in the group, including the incidence of questionable left ventricular enlargement by fluoroscopy. The lack of criteria to differentiate these 9 patients, even in retrospect, from those with demonstrated aortic regurgitation serves to emphasize the difficulty in evaluating the basal diastolic murmur by usual clinical methods. Unfortunately practical and reliable techniques for detecting pulmonary valve incompetence, especially of minor degrees, were not available to us during the study of these patients. Consequently no conclusions can be drawn in regard to the incidence of relative pulmonic regurgitation either as an isolated or as a coexisting lesion. These results indicate however that the great majority of patients with mitral stenosis and a basal diastolic murmur have aortic regurgitation regardless of the fact that the clinical evidence suggest relative pulmonic insufficiency. Similar results and conclusions have been achieved by others [23] using the same angiographic as well as other techniques.

We do not mean to infer from these studies that the Graham Steell murmur does not occur in patients with mitral stenosis or other forms of pulmonary hypertension. On the contrary the frequent disappearance of the basal diastolic murmur after successful mitral commissurotomy in those patients proved not to have aortic regurgitation lends support to its occurrence. Moreover the presence of relative pulmonic insufficiency has been conclusively proved by newer techniques which will be discussed later. Our results with aortic valvulography question only the previously reported incidence with which the Graham Steell murmur occurs in rheumatic heart disease, and emphasize the value of aortic valvulography in detecting unsuspected aortic regurgitation in patients with basal diastolic murmur considered for closed mitral valvulotomy.

In the clinical appraisal of the basal diastolic murmur associated with mitral stenosis there are certain confusing factors which are frequently overlooked and should be emphasized. As previously mentioned left ventricular enlargement which would normally suggest aortic regurgitation as the source of the murmur is difficult to evaluate radiographically in the presence of tight mitral stenosis. The displacement of the left ventricle posteriorly by the enlarged right ventricle may be misinterpreted on the lateral films as left ventricular enlargement. In the posteroanterior projection an oblique diameter of the cardiac shadow which exceeds the transverse diameter by more than 1.5 cm has proved to be a more reliable, although certainly not infallible index of left ventricular enlargement in adults. The electrocardiographic evaluation of left ventricular size is likewise difficult since the usual signs of left ventricular hypertrophy may be masked by coexisting right ventricular enlargement or an incomplete right bundle branch block.[23] If mitral regurgitation is a complicating lesion, the left ventricular enlargement even if present no longer affords a clue since it may develop as a result of either aortic or mitral insufficiency. The usual hemodynamic signs of aortic regurgitation as a result of increased left ventricular stroke volume and an accelerated diastolic runoff are frequently not evident in those patients with coexisting mitral stenosis. This may be due to a minimal aortic valvular lesion or it may be the result of a decreased left ventricular stroke volume due to the obstruction to left ventricular inflow. None of the 24 patients previously described exhibited a widened peripheral pulse pressure, even when 3+ aortic regurgitation was demonstrated by valvulography. In reference to pulmonary hypertension the intensity of the pulmonic component of the second heart sound although usually increased does not correlate well with the severity of the hypertension. A loud opening snap, especially in thin subjects, is often well heard at the pulmonic area and may be misinterpreted as a loud split pulmonic second sound leading the observer to erroneously suspect pulmonary hypertension. There is likewise only a fair correla

tion with the electrocardiographic evidence of right ventricular hypertrophy and the degree of pulmonary hypertension

Another important and frequently unrecognized problem in the clinical evaluation of basal diastolic murmurs is the occasional transmission of the diastolic murmur of mitral stenosis medially up along the left sternal border to even the second and third intercostal spaces in thin patients. Although this murmur is usually low pitched and rumbling it may on occasion be high pitched and blowing especially if there is calcification of the mitral valve It may also begin in early diastole and be decrescendo in character in patients with slow atrial fibrillation. If then the opening snap of mitral stenosis, heard at the base of the heart is mistaken for the pulmonic component of the second heart sound the observer may hear a typical high pitched blowing decrescendo diastolic murmur immediately after an accentuated pulmonic second sound and ascribe the murmur to pulmonic regurgitation We have been misled by this unusual chain of events on several occasions in patients who were later proved to have competent aortic valves by valvulography and normal or only slightly elevated pulmonary arterial pressures that were hardly consistent with a Graham Steell murmur In most instances the unusual character and transmission of the mitral diastolic murmur disappeared after successful surgical correction. This situation although infrequent must nevertheless be considered when one describes the disappearance of a Graham Steell murmur" after mitral commissurotomy

Fortunately there are some helpful clues in the evaluation of basal diastolic murmurs. Usually in mitral stenosis with pulmonary hypertension the aortic component of the second heart sound is decreased. If a basal diastolic murmur occurs with an accentuated aortic second sound, the murmur is more likely to be due to aortic regurgitation since an incompetent aortic valve is frequently associated with an increased intensity of its closing sound If the diastolic murmur is heard to the right of the sternum or if it is accompanied by an aortic systolic ejection murmur strong evidence for aortic regurgitation is provided Unfortunately both of the latter auscultatory clues are frequently absent in mild to moderate rheumatic aortic regurgitation As reported recently [24] a variation in intensity of murmurs with respiration (contrary to many previously held views) does not afford a reliable means of differential diagnosis.

Other techniques for evaluating the murmur Some of the shortcomings in the clinical appraisal of the basal diastolic murmur have been circumvented by the development of more objective means of evaluation including catheterization of the right and left sides of the heart indicator-dilution studies cardioangiography and intracardiac phonocardiography These techniques have improved considerably the selection of candidates for cardiac surgery and the subsequent results.

The level of the pulmonary arterial pressure when the right side of the heart is catheterized provides information in regard to the presence or absence of pulmonary hypertension but does not afford a means of confirming the diagnosis of a Graham Steell murmur In *organic* pulmonic regurgitation the pulmonary arterial pressure tracing demonstrates a characteristic steep slope of the dicrotic limb together with equal diastolic pressures in the pulmonary artery and right ventricle. This is not however a finding in *functional* pulmonic insufficiency

A variety of indicator-dilution studies have been developed in an attempt to localize regurgitant lesions. Many of these techniques involve analysis of the shape of the indicator-dilution curves, with either the injection of the indicator or the sampling of the indicator proximal and distal to the suspected valvular lesion Unfortunately these techniques are affected not only by regurgitant flow but also by the flow and volume of the blood within the segment of circulation studied as well as by intracardiac shunts. Furthermore these techniques are appropriate only for gross regurgitant lesions. Indicator-dilution studies that utilize the injection of an indicator substance distal to the valve with simultaneous sampling in the proximal chamber are better suited for detecting aortic and pulmonic regurgitation False-positive and false-negative findings still occur however

as a result of incomplete mixing of the indicator faulty positioning of the injection and sampling sites and distortion of valve leaflets by the catheter. Although more accurate than the previously mentioned indicator studies this technique is still unreliable for detecting minor degrees of valvular regurgitation.

The technique of aortic valvulography has been described in detail and its usefulness and reliability in detecting and grossly quantitating aortic regurgitation are well established.[4,33,34] The value of this technique is not limited to rheumatic aortic regurgitation. It has proved to be quite useful in the diagnosis of congenital aortic regurgitation Marfan's syndrome aneurysms of the sinus of Valsalva and the aortic regurgitation associated with ventricular septal defects. Pulmonic valvulography with injection of contrast media into the pulmonary artery via catheterization of the right side of the heart is less effective than aortic valvulography. It has been used to visualize marked regurgitation with congenital pulmonic insufficiency,[37,38] but it is not reliable for demonstrating the lesser degrees of functional pulmonic regurgitation with pulmonary hypertension. This is due primarily to distortion of the pulmonary valve leaflets by the catheter which often results in variable degrees of false-positive pulmonic regurgitation. We have demonstrated this in normal animals as well as in patients who were known to have normal pulmonary valves.

Intracardiac phonocardiography has proved to be a much more practical and reliable means for detecting pulmonic regurgitation.[39] The murmur of pulmonic insufficiency *functional or organic* is easily detected with the tip of the phonocatheter positioned at the right ventricular outflow tract, whereas the murmur of aortic regurgitation is not. We have been unable *to record aortic regurgitant murmurs of* even Grade 5 intensity from the right ventricle. This technique has also been useful in differentiating the syndrome of ventricular septal defect with aortic regurgitation from a patent ductus arteriosus, an aortic-pulmonary septal defect, and a ventricular septal defect with pulmonary hypertension and relative pulmonic insufficiency.[39] The absence of a continuous murmur with the phonocatheter in the pulmonary artery excludes the diagnosis of a patent ductus arteriosus or an aortic pulmonary septal defect. Detection of the diastolic murmur at the right ventricular outflow tract confirms the diagnosis of pulmonic regurgitation whereas the absence of a diastolic murmur in the right ventricle would indicate aortic regurgitation as the source of the diastolic murmur. This technique is certain to provide an excellent adjunct to the complete objective evaluation of the basal diastolic murmur but it still does not provide a means for quantitating the severity of the lesion.

Finally the administration of drugs has been utilized to help differentiate aortic from pulmonic regurgitation. The administration of sufficient norepinephrine to induce a significant increase in the systemic blood pressure causes an increase in the intensity of aortic regurgitant murmurs.[11] Unfortunately norepinephrine also raises the pulmonary arterial pressure and often increases the murmur of pulmonic regurgitation as well. Therefore it is not a reliable means for differentiating basal diastolic murmurs. Methoxamine[40] and mephentermine[41] have been used intravenously to increase the systemic blood pressure and the murmur of aortic regurgitation without affecting the pulmonary arterial pressure or the murmur of pulmonic regurgitation. Occasionally mephentermine may increase the murmur of pulmonic insufficiency as well if the heart rate is slowed sufficiently. Amyl nitrite on the other hand causes a fall in the systemic pressure and reduces the intensity of aortic insufficiency whereas the murmur of pulmonic regurgitation remains the same or is occasionally increased. It has been shown that serotonin administered intravenously increases the pulmonary arterial pressure without affecting systemic pressure and therefore accentuates diastolic murmurs on the right side without changing aortic regurgitant murmurs. These various techniques appear to be reliable but further studies should be undertaken with more objective confirmation of the source of the murmur being evaluated.

Surgical implications. It is apparent that detection of the aortic regurgitation associ-

ated with a ventricular septal defect is essential if this syndrome is to be differentiated preoperatively from the other lesions which may simulate it. The practical significance of objectively differentiating adynamic aortic regurgitation from relative pulmonic insufficiency in patients with mitral stenosis is not so clear. Adynamic aortic regurgitation, if present, is often considered to be physiologically insignificant and hence not a contraindication to closed mitral commissurotomy. Our experience has not always supported this view. We have seen aortic regurgitation of 2 and 3+ severity as demonstrated by aortic valvulography without evident left ventricular enlargement or the usual peripheral dynamics. Mitral commissurotomy in these patients has often resulted in either no improvement or a deterioration of the patient's course after operation. Others[12,13] have also commented upon the deleterious effects of aortic regurgitation after mitral valve surgery. Whether the poor results in these patients are directly related to the aortic regurgitation or merely reflect a more severe form of rheumatic heart disease is not yet settled. However, it seems reasonable to assume that, with other factors constant, an augmented left ventricular flow after mitral valvotomy may result in an increased severity of the aortic regurgitation. We have observed a definite increase in the degree of aortic regurgitation after mitral commissurotomy in 2 of 7 patients in whom aortic valvulography was performed both preoperatively and postoperatively. Four other patients who were carefully evaluated preoperatively developed a basal diastolic murmur for the first time shortly after mitral valve surgery and were proved to have aortic regurgitation by valvulography. This "unmasking" of aortic regurgitation has been noted by other observers,[14] but the aortic regurgitation was not objectively confirmed. These experiences lend support to the view that aortic regurgitation may be increased after relief of the mitral valvular obstruction and thus may affect adversely the results of mitral valvotomy. Experimental work has further suggested that the untoward effects of coexisting aortic regurgitation may be intensified if mitral regurgitation is inadvertently produced or increased at the time of operation.[15]

The indication for surgical intervention in isolated organic pulmonic regurgitation is also unsettled. Experimental pulmonic regurgitation in dogs has produced variable results, but some of the long term studies have shown that the lesion can produce right ventricular enlargement[16] and congestive heart failure[17] and thus may not be entirely innocuous. It is difficult to arrive at definite conclusions concerning its effects in man, since the necessary clinical studies are limited by the rarity of the isolated lesion. In general, however, organic pulmonic regurgitation is apparently well tolerated, even into the seventh decade, unless complicated by other cardiac or bronchopulmonary disease.

It appears that, although there have been major advances in methods for determining the origin of basal diastolic murmurs, there is much less information in regard to the physiologic significance of these murmurs. This is particularly true for adynamic aortic regurgitation in patients with mitral stenosis. What degrees of aortic regurgitation will still permit a successful closed mitral commissurotomy, and what effect mitral commissurotomy has upon coexisting aortic regurgitation are still not definitely determined. Whether surgical correction is indicated in isolated organic pulmonic regurgitation is also unanswered. Hopefully, these and other problems associated with the basal diastolic murmur will be solved with reliable long term objective studies in the future.

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tion seemed inevitable in one patient (Case 8) on two separate occasions when her congestive failure recurred in spite of oral and parenteral diuretics restriction of fluid digitalis and dexamethasone. The other patient (Case 13) had anasarca due to carcinomatosis secondary to a uterine malignancy and probable cardiac metastases. Her initial dramatic diuresis over a 3-day period after the institution of digitalis parenteral mercurials and formula was sustained when small doses of spironolactone and an oral diuretic were given for 4 more days—resulting in a diuresis of 18 pounds within 1 week.

This dietetic program also proved to be of value in the management of marked *edema of the lower extremities* in 3 individuals who did not have heart disease. Two patients (Cases 15 and 16) were moderately or markedly obese and had chronic postphlebitic syndromes. The other patient (Case 14) a woman with longstanding rheumatoid arthritis that involved the knees had incapacitating lymphedema of the lower extremities but was not otherwise overweight. The ease with which it was possible to induce a regression of her lymphedema on formula the previous oral diuretic and intermittent periods of rest and to subsequently rehabilitate her is all the more noteworthy since she still required moderately large doses of an *adrenocortical steroid which tended to* maintain her edema. The extra mobility allowed Cases 14 and 15 was also desirable as a means of precluding further demineralization of their osteoporotic vertebrae.

The success of simultaneously instituted *weight reduction* programs centering about the use of such a food formula is evidenced by the representative case histories to follow. The average total loss of weight from the initiation of Phase I (formula alone) to the arbitrary conclusion of Phase III (i.e. the ingestion of a standard hypocaloric diet) in the 9 obese individuals in this series was 27 pounds (ranging from 14 to 47 pounds). The time required for achieving their lowest weights ranged from 21 to 270 days averaging 82 days.

The *side effects* encountered with the use of Metrecal have been considered elsewhere in detail[7,8] In this series of patients, however they were minimal—perhaps because of previous experience with its administration. Patients were advised to take a mild laxative (e.g. milk of magnesia) if they were concerned about temporary constipation. A mild antacid-antispasmodic preparation was given for any gas bloating or heartburn. One patient (Case 12) lost from 150 to 146¼ pounds within several days after the formula was instituted for progressive congestive failure that had resisted therapy with prednisolone and spironolactone. He then experienced a bout of severe nausea and vomiting which was attributed to the formula. Subsequently he was maintained on a salt-poor diet and limited fluids. He again experienced nausea on a further attempt to take formula as a result of which it was withheld. Several patients found that the formula began to repeat (with or without nausea) after they had been on it for 1 week or longer—but during which time most of their edema had subsided. One patient found that equal parts of formula and milk were better tolerated under these circumstances.

When one considers the fact that most of these patients were in an older age group the absence of both undue fatigue and psychiatric aberrations was impressive. Even the patient with carcinomatosis felt and looked better than she had in months. Probable hepatic hypoglycemia was a *prominent consideration in Cases 9* and 21 but was checked by adequate or frequent servings of formula. Longstanding recurrent hypoglycemia due to diabetes mellitus posed a major problem in Case 20 but was readily controlled with frequent feedings. There was no evidence of anticoagulant escape in those patients who also were being maintained on long term anticoagulant therapy. The precipitous gain in weight noted by others when patients resumed natural food after having been on a 900-calorie liquid diet—attributed to shifts in the extracellular fluid—was not observed.[9]

Case Reports

Case 1. Successful treatment of congestive failure in an obese patient with gout and diabetes mellitus concomitant obesity management. (*Fig. 1*). G. M. a 72 year-old retired physician presented with progressive heart failure on May 2 1961. It was characterized by several weeks of recurrent *nocturnal*

Narcotic analgesics in heart disease

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The acute pain of ischemic heart disease and the much less common chronic pain of aortitis represent the major pain problems in heart disease. For the most part these are severe and beyond the scope of mild analgesics. In addition to the need to relieve the suffering of the patient, it is important to control this symptom because of the further noxious effect of pain on cardiovascular responses.

The potent narcotic analgesics remain the only drugs adequate for the treatment of cardiac pain despite side effects which can cause serious problems in the cardiac patient.

When given in therapeutic dosage these drugs may variously produce respiratory depression, nausea and vomiting, constipation, gall-bladder colic, dysuria, bronchospasm, tachycardia and arrhythmia, tolerance and addiction.

Some of these adverse effects are produced by morphine and its congeners, others by meperidine and its congeners, and some by both, although chemically very different. Methadone produces side effects similar to the morphine group. The derivative drugs within each group are not qualitatively different from the parent drugs, so that morphine and meperidine can still serve as prototypes for discussion.

Respiratory depression. Excessive respiratory depression due to a direct effect on the respiratory center is the most serious complication of these drugs. Although some respiratory depression is helpful in the patient with hyperventilation or pulmonary edema, a greater degree in a patient with circulatory or pulmonary insufficiency can be a life-threatening complication. In normal man there is measurable respiratory depression after as little as 5 mg. of morphine. In patients with cardiac pain, however, considerably larger doses are tolerated without respiratory depression. Some late depression may be due to a change in the state of the patient as the pain is relieved. Often, however, such late depression is due to the cumulative effect of the drug as the physician prescribes frequent and increased doses to control severe pain, losing sight of the delay in effect after even intravenous administration and of its increasing effect over several hours. Therefore, it is safer in situations of refractory pain to attempt to diminish pain to the point of acceptability rather than to eliminate it. Meperidine is not so potent a respiratory depressant as is morphine, but the significant effect of meperidine and its congeners on respiration provide a real hazard.

Nausea and vomiting. Nausea and vomiting commonly occur after narcotic analgesics and are due to stimulation of the central nervous system. None of the drugs now available is free of this effect, nor is there evidence that any one is preferable to the others in this regard despite claims to the contrary. The tendency to-

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ward emesis is an individual idiosyncrasy with these drugs. There is no predictable pattern in the responses of patients susceptible to the various agents. Certainly a patient should not receive the drug which has caused emesis previously and other agents should be used with caution in such patients because of the likelihood of similar response. Narcotic induced emesis can usually be relieved by chlorpromazine but the routine prophylactic use of chlorpromazine is not recommended because of the special danger of its hypotensive effect in the cardiac patient as well as its other toxic manifestations.

Effects on smooth muscle. Constipation, dysuria, gall bladder colic, and bronchospasm are due to a direct effect of morphine on smooth muscle tone. Meperidine has no significant effect on smooth muscle tone in the gastrointestinal tract. Morphine may also produce bronchospasm by releasing histamine, making its use especially hazardous in the asthmatic patient. In this respect meperidine has an advantage over morphine. If anything, it exerts a feeble spasmolytic effect on the bronchial musculature.

Meperidine, however, produces cardiac acceleration through a vagolytic action. Morphine tends to slow the heart through central vagal action. Cardiac arrhythmia is also seen after meperidine. In these two aspects, its value may be inferior to that of morphine in the cardiac patient.

Tolerance and addiction. Tolerance and addiction are infrequent complications of these drugs when used for acute myocardial infarction and occur only in former addicts or in the very unstable individuals with a high addiction liability. Addiction is common when the drug is used for more than 2 weeks, however.

Despite various claims, there is no substantial difference in the addiction liability of any of these drugs. Phenazocine, which was thought a few years ago to be different in this regard, has been shown to have no advantage over morphine. Meperidine causes many more cases of accidental addiction because it is used with much less caution than morphine by the medical profession.

Derivatives of morphine and meperidine. Within the morphine group (see Table I) differences are primarily in dosage. In some, smaller doses are used, but in maximum safe doses, none will relieve more severe pain than morphine. Some have a slightly more rapid onset of action than

Table I

Group	*Drug*		*Approximate equianalgesic dose (mg.) subcutaneous*
	Generic name	*Proprietary name*	
Morphine and congeners	Morphine		10
	Codeine		60
	Dihydrocodeine	Paracodin	30
	Dihydrocodeinone	Hycodan	15
	Dihydromorphinone	Dilaudid	2
	Levorphanol	Levo-Dromoran	2
	Oxymorphone	Numorphan	1
	Pantopium	Pantopon	20
	Phenazocine	Prinadol	2 5
Methadone and congeners	Methadone	Dolophine	10
	Dipipanone	Pipadone	10
Meperidine and congeners	Meperidine	Demerol	100
	Alphaprodine	Nisentil	50
	Anileridine	Leritine	40
	Piminodine	Alvodine	10

does morphine, but with no practical advantage. Because of rapid destruction by the liver none is very effective by mouth.

Methadone differs from morphine only in fairly good oral activity

The current popularity of meperidine and its congeners cannot be accounted for by any proved virtue They are highly addictive cause respiratory depression induce nausea and vomiting and are not so potent as morphine. Regardless of dose they cannot relieve some severe pain that responds readily to morphine

Given by mouth they produce inconstant effects. When assurance of activity is necessary they must be given parenterally

Chest ache

A frequently a female patient will come to a cardiologist for an explanation of fixed functional heart pain. Often she has been seen by many physicians and has derived little satisfaction from them. She presents herself or is referred for a final definitive answer. Confronting the cardiologist is the problem of allaying her fears, sympathetic acceptance of the existence of pain, and imparting a credible but satisfying explanation of the distress. When an analogy is made comparing the chest pain to a headache, the finding consistently has been that the patient is better able to understand functional chest pain, and that her fear of underlying heart disease is greatly reduced.

It is most important when a physician first sees such a patient that he initially obtain a complete history, make a complete physical examination, and do the necessary laboratory work. This is not only for his reassurance that organic disease is not present but for the reassurance of the patient as well. Often the chest pain may be a fixed complaint of several years. A patient may challenge the consultant by saying that she knows that it is not in her head or that it is not her nerves as the other doctors have told her. To attempt to examine her superficially and to say everything is normal or to attempt to delve into deeper psychiatric description will be equally ineffective.

After the patient has been interviewed and examined the analogy to headache is clearly impressed on her. In beginning the description, one might ask her initially whether she has had headaches. If she has experienced them, it is pointed out that her chest ache is similar to a headache. As she knows, headaches may be very severe and they tend to come and go. Stress or anxiety may aggravate them. But also as she well knows, people live out their normal lives with them and in the case of the common headache there is nothing abnormal inside the head, nothing wrong with the brain. The same applies to her chest ache. There is nothing wrong within the chest. The heart and lungs are normal. Just as occurs with headaches, the pain may be very severe at times. It will come and go, tension may aggravate it, and aspirin often is beneficial. Should a patient say she does not suffer headaches, she is told that perhaps she is the type of person subject to chest aches rather than headaches, and the comparison is again carefully made.

Without exception the foregoing description has been of great comfort to the patient with functional chest pain and invariably no further explanation is sought. By analogy the patient grasps the significance of the pain in the chest wall and understands that it is not her heart that is malfunctioning. On follow-up visits, when inquiry is made about the functional pain, the term "chest ache" should be used by both the physician and patient. Within a relatively short time the patient is able to manage her chest ache by herself and the severity of the pain as well as concern over it rapidly diminish.

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The genesis of the third heart sound

The diastolic events of the left side of the heart in mitral valvular disease have been studied at cardiac catheterization by means of simultaneously recorded phonocardiograms, left atrial and ventricular pressure pulses, and displacement curves of the left ventricular apex. In all varieties of mitral disease irrespective of whether the lesion impedes or enhances ventricular filling, a particular event takes place 0.1 to 0.17 second after the closure of the aortic valve. It is manifest in the sudden deceleration of the left atrial "y" descent at the annular ascent point and in the sudden reduction in the rate of the outward movement of the left ventricular apex at the third sound point. The observation of the heart at operation and published work,[1,2] suggests that this event is the vigorous early diastolic elongation of the left ventricle. In cases of severe mitral incompetence with atrial fibrillation in which

surgical exploration has excluded any element of stenosis the tracings show that three other events occur synchronously with the ascent of the annulus fibrosus, namely the third heart sound the onset or the sudden waxing of the diastolic murmur and the brief inward movement of the left ventricular apex that is recorded when third sound is present.[1] They take place hen the left ventricular filling pressure gradient is close to maximal, about ½ to ⅓ second before the equalization of the left trial nd the left entricular pressures in diastase.

These facts are accommodated best by the following theory: During the cardiac cycle the apex of the left entricle alters little in position. I systole, ventricular contraction moves the atrioventricular ring toward the pex of the heart, and, in early diastole, igorous longation of the ventricles causes the base suddenly to ascend.[1,2] When the left ventricle is distended ith blood, the distance from the base to the pex increases, but the mitral cusps and chordae do not elongat Consequently when the ventricle is distended beyond certain point, igorous longation suddenly tenses the mitral cusps and chordae and produces noise—the third heart sound traction on the cusps and chordae pulls inward the pex of the left ventricle—the movement recorded hen third sound is present. The anatomic arrangement of the chordae ensures that their tautening reduces the mitral orifice nd causes degree of obstruction to trioventricular flow The sudden onset of degree of obstruction checks entricular filling, reduces the rate of y descent, and slow the outward movement of the pex of the left entricle When the left trium still contains excessive amount of blood under high pressure, the sudden check causes the onset or the axing of the diastolic murmur

Most authors agree that the pathologic third heart sound is an exaggeration of the physiologic third heart sound.[3-8] This is suggested by the fact that they both occur t the nnular ascent point of the left trial pulse[1] in association with an inward movement of the pex of the left entricle, and ith rightw rd and headward force that may be seen on the ballistocardiogram Analysis of the sounds show similar frequency patterns.[9,10]

It ma be asked hether the third sound marks normal event occurring in every heart cycle, or whether it is caused in health and disease by special conditions hich are present t some times nd not t others third heart sounds are udible in the majorit of normal oung people [11,12] nd the vibrations ca usually be recorded in health when they are too quiet to be heard th the stethoscope.[5,13,14,15,16,17] Therefore t seems likely tha normal even in the cardiac cy le occurs the time of ann lar ascent nd causes vibrations hich may be inaudible udible in health the physiologic third sound or udible in disease as the pathologic third heart sound

The earliest observers[18-20] of the hird sound believed that its vibrations originated in the sudden tensing of the mitral cusps and chordae and Dock ent fa to support beh hen he demonstrated that the forces required to evok ud ble sound from ventricular muscle re grea ly in excess of those present in living nimal Rushmer[4] ha show that in life the excursion of the mitral cusps is not so great as is popularly supposed the edges of the leaflets move small amount that is consistent ith the valve being tensed and relaxed by muscular action and blood flow in the arious phases of the cardiac cycle. The ell-known changes in the loudness of the third sound with the severity of the heart disease [20,21,22,23] and with changes in posture and blood flow [21,22,23,24,25] may be caused by lterations in left ventricular distention varying the tautness of the fibrous parts of the mitral alv t the onset of the elongation. The reason for the loudness of the third sound in thletes and normal young people is matter for speculation perhaps their left ventricular residual olume is relatively great.

Crevasse[26] and his colleagues confirmed Kuo s[27] observation that the third heart sound occurs hen the trial pressure is higher than the entricular and showed that under certain conditions, the third sound may be absent from the trium when it can be recorded from the entricle Their findings do not ppear to be inconsistent with the thesis presented here.

Potain[28] considered that the dilating ventricle q ickly reaches point t which the fibrous resistance of its wall limits its distention and the latter sharply arrested, causes tension, shock, nd the gallop sound. It is high time that cardiologists bandoned this concept of the ventricle ts tening nd producing sound like a blown-up paper bag because many careful studies have recorded the third heart sound during the period of ventricular filling, and not t its end [1,4,20,29,30] and Dock[31] has demonstrated that in lif the ventricle is capable of distending far beyond the size t which third sounds occur

It has been suggested that the third heart sound and the mitral opening snap are one and the same,[32,33] but the two sounds ha been recorded in one heart cycle too often for this view to be maintained. The theory that the third sound is caused by the impact of the heart against the chest wall is disproved by those observers who have heard or recorded it in the exposed heart.[34]

The other ork which bears upon the genesis of he third heart sound has been reviewed recently

T summarize the ailable evidence suggests that the third heart sound ibrations arise when the igorous early diastolic elongation of the left ventricle suddenly tautens the mitral cusps and chordae. The loudness of the sound depends upon the mitral tension in the valve fibers function of the volume of blood ithin the entricle nd pon he force nd magnitude of the elongation.

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Pulmonary stenosis. The importance of the myocardial factor in determining the clinical course and surgical results

Isolated pulmonary stenosis, in the absence of overt signs of right ventricular hypertrophy, is often considered to be a relatively benign congenital lesion. This concept of benignity stems from preoccupation with the absence for many years of significant or incapacitating symptoms despite severe obstruction. Such a concept ignores the detrimental effect on the integrity of the myocardium of long-standing obstructive valvular disease. Considerable clinical and pathologic experience, however, has accumulated to demonstrate that many patients whose pulmonary stenosis has escaped early detection and surgical relief receive suboptimal improvement when operative intervention is eventually undertaken.[1-3]

Such a course was demonstrated by W. M. [illegible], a [illegible]-old white man, who was first admitted to the Duke Medical Center in 19[illegible]. The patient gave a long history of known heart murmur, dyspnea on exertion, and palpitations. Despite these symptoms he worked regularly as a farmer. Physical examination revealed moderate cardiomegaly, a right ventricular heave, and a prominent basilar systolic thrill. The pulmonary closure sound was [illegible], with an aortic-pulmonary interval of 0.1[illegible] second. An ejection-type systolic murmur of late onset was heard maximally over the pulmonary area.

The electrocardiogram demonstrated first-degree heart block, right axis deviation, with right ventricular hypertrophy and strain. The chest x-ray film confirmed gross cardiomegaly and revealed poststenotic dilatation of the pulmonary artery. Catheterization of the right side of the heart confirmed the impression of isolated pulmonary stenosis. The right ventricular [illegible] pressure was 106 mm. Hg, with a transvalvular gradient of 90 mm. Hg.

At operation, an extraordinary degree of right ventricular hypertrophy was found. So enlarged was this chamber that the dilated pulmonary artery appeared to arise from the left lateral aspect of the heart. Palpation of the valve ring revealed a pronounced thrill due to jet-like ejection of blood through an orifice approximately 5 mm. in diameter. The right ventricular systolic pressure was 100 mm. Hg. A valvulotome was passed through a small ventriculotomy incision, and the pulmonary valve opened to an estimated 2 cm. After this procedure the right ventricular pressure was 40 mm. Hg.

After the operation the patient was seen periodically in the Cardiac Clinic. His work tolerance was restricted [illegible] [illegible] from chores. Physical examinations showed persistence of cardiomegaly with a right ventricular lift. Auscultatory findings were unchanged. Interval electrocardiograms and chest x-ray films showed no significant improvement. In September 19[illegible], he developed atrial fibrillation and was rehospitalized.

Cardiac catheterization was performed [illegible]. The right ventricular pressure was 45 mm. Hg; the gradient across the pulmonary outflow tract was [illegible] mm. Hg. The cardiac output by the indicator-dilution technique was [illegible] L. per minute.

Angiocardiographic demonstration [illegible] gross enlargement of the right atrium and ventricle, slight encroachment on the right ventricular outflow tract by a hypertrophied infundibulum, and dilatation of the pulmonary artery. Clearance of the contrast medium from the right side of the heart was markedly prolonged.

In summary, the patient demonstrated greatly impaired cardiac function, despite satisfactory relief of pulmonary valvular obstruction [illegible] years previously. Cardiomegaly persisted. The electrocardiographic abnormalities indicative of right ventricular hypertrophy and strain remained unchanged. Atrial fibrillation developed. The cardiac output was inordinately low.

The practical implications of these observations are compelling. This patient demonstrates that the right ventricle cannot work indefinitely against significant outflow obstruction and retain the ability to compensate after the relief of obstruction. Even after obstruction is relieved, the hypertrophied but "strained" ventricle may not be able to eject a normal stroke volume.[1-3]

Mauck and Campbell[4] demonstrated diffuse fibrosis of the right ventricular myocardium in the hearts of patients with congenital pulmonary valvular stenosis and intact interventricular septum. Such pathologic changes are not unexpected. Simple calculations indicate that, in order for the cardiac output to double during exercise in patients with a valve area of 0.5 sq. cm. or less, the ventricular pressure would have to approximate 300 mm. Hg. However, the majority of patients with moderate or severe pulmonary stenosis have a low-normal or reduced cardiac output. Therefore, the rate of rise in pressure through progressively narrower pulmonary orifices is retarded. The peripheral needs for increased flow in such patients must be met by increased oxygen extraction. Such a defense is poorly tolerated by the hypertrophied myocardium.

There is generally a tendency for the clinician to ignore the significance of mild stenosis (right ventricular pressure below 5[illegible] mm. Hg). Patients with severe stenosis (right ventricular systolic pressure above 1[illegible]0 mm. Hg) are usually considered to be candidates for immediate operation. Not infrequently, operation is postponed for the intermediate group of patients with moderate stenosis (right ventricular systolic pressure between 5[illegible] and 1[illegible]0 mm. Hg).

Little benefit is provided to patients with moderate stenosis by rigid [illegible] preconceived concepts in regard to the indications for pulmonary valvulotomy

Notwithstanding the observation that, in general, older patients have derived less than optimal results from operation, it is unjust to conclude that youth protects the myocardium.

The finding of significant pulmonary stenosis in patients who survive beyond the fourth decade is unusual. Results may be less than optimal when operation is carried out during middle or late life. In a series of 30 consecutive patients operated on for pulmonary stenosis at the Duke Medical Center, 1 has died in the postsurgical period. This was a 42-year-old man who developed heart failure prior to operation and died several weeks after an apparently uncomplicated valvotomy. His course was one of steady downhill despite relief of the valvular stenosis. This experience further emphasizes the deleterious effect of long-standing outflow obstruction on cardiac performance.

There is a point in both the magnitude and the duration of obstruction after which surgical relief cannot be expected to result in restoration of normal cardiac function. This point cannot be predicted in a given patient. The operative technique for the relief of such obstruction has greatly improved, and surgical mortality and morbidity have greatly decreased. It is our current belief that patients with isolated pulmonary valvular stenosis who have normal or reduced flow and transvalvular gradients of 40 mm Hg or right ventricular pressure above 65 mm. Hg should be considered for surgery without undue delay. When such excellent surgical results may be expected, it appears likely that the status of the myocardium is the final determinant of the clinical course and prognosis of pulmonic stenosis.

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Anticoagulant therapy in acute myocardial infarction

The early studies of anticoagulant therapy produced good statistical evidence of its value in the prevention and treatment of venous thrombosis and pulmonary embolism. This evidence has been supported by later studies on surgical and gynecological operation cases, parturient women, and patients suffering from fractured femora and from acute myocardial infarction.[1-5]

In the case of venous thromboembolism the problem examined is a limited one and does not make excessive demands upon the statistical method. The condition studied is the same in all the different types of clinical material; it is relatively easily recognized and it is clearly related to the thrombotic process which the treatment is designed to combat. Finally the results reported are remarkably uniform in the various studies, even though these differ in their other conclusions.

The evidence relating to systemic arterial embolism, although less extensive, is similar in character. It shows that anticoagulants have a prophylactic value against embolism although their value in therapy is much less clear.[6-10]

The evidence in support of the use of anticoagulants in the prevention and treatment of venous thromboembolism and systemic arterial embolism can therefore be accepted and the measure of benefit to be expected can be fairly weighed against the possible risks of the treatment.

The evidence in regard to acute myocardial infarction is much less satisfactory. It does support the effect of anticoagulant against the types of thromboembolic complication already mentioned. However in most of the studies on myocardial infarction the enquiries have been formulated on a much wider basis. The concept "thromboembolic complications" has been expanded to include secondary myocardial infarction, i.e. extensions of the original infarcted area or new areas of infarction in the myocardium. There are some theoretical difficulties here. It is now well recognized that myocardial infarction often occurs in the field of distribution of a narrowed coronary artery without any thrombotic occlusion of the vessel, probably by reason of functional depletion of the local supply of blood conditioned by variation in arterial blood

pressure. For example Wright and associates recognized 24 secondary myocardial infarctions among their 91 autopsies, but new thrombus could be demonstrated in less than half of these secondary infarctions. Nevertheless, they included all such instances of secondary infarction whether diagnosed clinically or at autopsy under the heading of "thromboembolic complications" and presumed them all to be potentially preventable by anticoagulant therapy. A considerable number of these secondary infarctions appear to be unrelated to thrombosis.

In most of the studies of myocardial infarction the basis of assessment has been widened still further by using the over-all death rate as a measure of the value of the treatment. This approach has so complicated the problem as to raise some doubt whether the statistical method can justifiably be applied. The death rate in acute myocardial infarction is influenced by many different factors, and a fair comparison between two series of cases is extremely difficult. This is illustrated by the widely different death rates in different series treated without anticoagulants, ranging from 16 per cent to more than 50 per cent.

In many studies the method used is to compare over-all death rates in two groups of patients, one group routinely treated with anticoagulants, the other group treated without them. This method lays on the investigator the responsibility of ensuring that the two groups of patients are similar in all respects, apart from the use of anticoagulants in treatment. The infinite variety of human patients in their reaction to disease and of human medical institutions in their attitude toward treatment makes this almost impossible. Selection factors beyond the control of the investigators will influence the character of the two groups in ways which cannot be corrected by the most careful analysis. To take examples from the many published studies, one pair each from the U.S.A., Great Britain, and Denmark, Wright and associates, Tulloch and Gilchrist, and Holten all reported a considerably lowered death rate with anticoagulant therapy, whereas Eastman and associates, Honey and Truelove, and Hilden and associates could not show any significant effect.

A series of investigations of this type has shown lower death rates in anticoagulant-treated cases than in controls, but in many of them the selection factors appear to have affected the constitution of the two groups in such a way as to raise doubts about the validity of the results. For example, Wright and associates, in a study of 1,031 patients, concluded that the death rate could be reduced from 23 per cent to 16 per cent by routine anticoagulant therapy. This study has been widely regarded as authoritative, but critical examination of the data in the report raises many doubts. First, the attempt to secure random selection of patients by allocating them to "treatment" and "control" groups according to odd and even dates of admission to hospital was not successful. The disparity in numbers of the two groups ("treatment," 589; "control," 442) indicates that this rule must have been disregarded on many occasions. The authors suggested that in some cases the referring physician may have accelerated admission to hospital to ensure admission on an odd date and so secure the expected benefit of anticoagulant treatment. Secondly, the evidence in the report shows that in the first week of illness there was a higher incidence of signs of heart failure in the control group than in the treatment group. Thirdly, the cases studied were distributed in 16 different hospitals, situated in 9 different States, and were observed under the responsibility of 19 different investigators. This must have rendered coordination of the conditions of hospital care extremely difficult, and the report gives little indication of any standardization in this respect.

The type of hospital care given was not uniform. The patients studied included both public ward cases and private cases, very unequally distributed among the 16 hospitals. Death rates were consistently lower in private cases than in public ward cases both in controls (19.8 and 25.2 per cent, respectively) and in treated cases (11.4 and 19.4 per cent, respectively). In fact, the difference in over-all death rates between private cases (14 per cent) and public ward cases (21 per cent) is slightly greater than that between anticoagulant-treated cases (16 per cent) and controls (23 per cent). The authors suggest that the lower death rate in private cases may have been due to the higher standard of nursing care which they received, but it seems likely that it was due largely to a higher proportion of mild cases of myocardial infarction. Wealthier patients tend to seek medical care for mild symptoms more readily than do patients of lower economic status, and this tendency is increased by the private insurance for medical expenses commonly held in the United States. If we confine the comparison between treated cases and controls to the 8 hospitals which contributed only public ward cases, we find that the difference in death rates is negligible (172 treated cases, death rate of 18.6 per cent; 136 controls, death rate of 19.8 per cent). Similarly, if we confine the comparison to the two hospitals which contributed private cases almost exclusively, the difference in death rates is again small (149 treated cases, death rate of 14.1 per cent; 107 controls, death rate of 17.7 per cent). In the other 6 hospitals, which had substantial numbers both of private and of public ward patients, the difference in death rates was much more striking (268 treated cases, death rate of 15.3 per cent; 199 controls, death rate of 25.1 per cent). These results suggest that the death rates were unequally affected by factors other than anticoagulant therapy. There are grounds, therefore, for doubt as to the true comparability of the treatment and control groups in this study.

The study made in Copenhagen by Hilden and associates is comparable in the numbers of patients to that of Wright and associates. It was confined to 2 hospitals of similar type in the same city and was carried out by 4 investigators in close and continuous collaboration. Some statistical criticisms have been made of this study, but its material is more uniform and there appears to have been much better standardization of the general conditions of hospital care than in the American study. The Danish workers found no significant difference in over-all death rates between the control group and the group treated with anticoagulants (25 and 23 per cent, respectively).

There mu t be some scientific doubt, therefore about the statistical evidence appearing to show a considerable lowering of over-all death rate in myoc rdial infarction by the routine use of ntv-coag la t therapy The evidence show ng a re-duc ion in the incidence of enous thromboembolism cceptable but this complication is responsible for only small part of the total death rat More-over an be combated by other means especiall mebas treatment nd earlier ambulation.[11, 12] The use of anticoagulants may justifiably be con idered selected patients who ppear t ha pecial liabilit t enous thromboembolism for xample obese patient those with previous his-tory of nous thrombosis and those who for some on ha t be confined to bed for longer periods.

A factor which must be carefully weighed is the degree of risk in olved in the treatment tself The effect of such risk rises to maximum when the treatmen is employed routine in all cases It not be denied that there are risks in the thera peu ic se of anticoagula ts, nd these risks are not elimina ed even by the most conscientious control of prothrombin levels.[17-20] Physicians who use anti coagula therapy must accept the fact that cert mber of their patients will suffer hemor rhag nd hat small proportion of these pa ien the hemorrhage will be fatal. Wright nd associ es discussed this problem, and their pro-nouncement must be quoted slightly less than tw more deaths w th haemorrhage or rupture major or contributing cause per hundred cases can probably be expected w th anticoagulant therapy than without t This regrettable loss fortunately is con erbalanced by substantially lower expecta-tion of dea h due thromboembolism w th than without ticoagula t protection As a result the net sa ng lives associated with ticoagula t therapy reported in Chapter XI was about 7 per h ndred hospitalized cases of myocardial infarction

This is extremely d bious ethical position for any ph sician. I plain terms it means that t is justifiable t sacrifice certain patient in the hope of sa ing larger umber of others. Anyone who has an bsolute certainty of the validity of the sta tistical evidence may perhaps be able to reconcile himself t this proposition so long he considers it purely in sta istical terms. H must surely suffer misgivings if he tries to pply it in the case of individual patient

The ethical difficulty arises only when *each* ticoagula t therapy is in question. I the case of y ind idual patient it is quite proper to balance the risk of thromboembolism against the risk of possible hemorrhage nd t reach decision based purely on that patient i terests. Russek[21] has pointed out that there are ma y "good-risk" cases of myocardial infarction in which the risk of throm boembolic complications is ery small. It is surely questionable practice t employ anticoagula ts as routine treatment nd to accept the risk of f tal hemorrhage in such patients for the sake of benefits which may be gained only by others.

This ethical difficulty reinforced by doubts of the validity of the statistical evidence should weigh heavily against the routine use of anticoagula ts in patients who are suffering from acute myocardial infarction When each patient s needs are considered individually there will be a certain number in whom the use of the treatment is justified.

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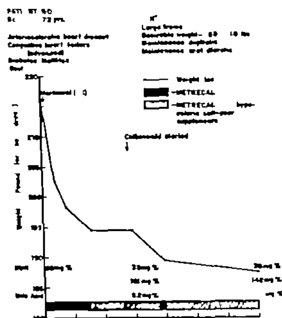


Fig. 1. See text.

dyspnea, tachycardia, frequent ventricular premature beats, extensive bibasilar râles, and enlarged tender liver which extended four finger breadths below the costal margin. He had been taking digitalis whole leaf (0.1 Gm.) and chlorothiazide (250 mg.) daily. H weighed 215¼ pounds. H was 5 feet 11 inches tall and of large body frame. His initial blood urea itrogen was 60 mg. per cent.

The patient was given single injection of mercurial diuretic was advised to increase the dose of chlorothiazide t 500 mg daily and was placed on formula as his sole diet. By May 4 his weight had decreased to 202¾—a diuresis of almost 13 pounds in 2 days. He volu teered that he was feeling much better and had experienced only minimal weakness. Striking regression of the pulmonary congestion and hepatomegaly had occurred. He was advised t continue on formula (one glass t 8 A.M one glass t 5 .M one-half glass t bedtime, one-half glass t 2 A.M.) and to take glass of orange juice t noon. By M y 6, his weight had declined t 198¼ pounds, and further clinical improvement was evident. His program was then modified by the use of other hypocaloric supplements, including Metrecal pudding nd wafers.

The patient thereafter had brief ttack of pain in the left knee, which complaint he had experienced intermittently for several years. His uric acid was found t be 8.2 mg. per cent. Colbenemid was added t his program. A fasting blood sugar also was found to be 161 mg per cent

On June 22, his eight was 187½ pounds. He volunteered that he felt better than he had in many years, and that there ere no further symptoms in the joints. There ere declines i the uric acid to 5.85 mg per cent in the blood rea itrogen to 30 mg per cent and i the fasting blood sugar to 142 mg per cent The patient continued his previ ou digitalis dosage, but was able t stop chlorothiazide completely nd uneventfully as of 8 months later

Case 2 Successful management of congestive f ilure concomitant obesity management. (*F g 2*). R. H., an 83-year-old retired white man, had been treated several months previously for an acut myocardial infarction that was complicated by mild congestive failure His convalescence was further complicated by progressive gain in weight—viz., from 195 pounds on Feb. 11 1961 to 216¾ pounds on April 22, 1961 H had large body frame nd was 6 feet tall. With this gain in weight extensiv bibasilar râles, congestive hepatomegaly and moder te peripheral pitting edema of the lower limbs had developed H had been taking digitalis whole leaf (0 1 Gm. daily) and hydrochlorothiazide (50 mg three times weekly) since his acute myocardial infarction.

The dosage of hydrochlorothiazide was increased to 100 mg daily but that of the maintenance digitalis was continued. One injection of mercurial diuretic lso was administered. He was placed on formula as his sole diet supplemented by limited amounts of water By April 29—1 week after initi tion of the above-described program—his weight had declined by 12¾ pounds to 203¾ pounds. There was marked clinical improvement, the patient experiencing only moderate weakness with his profound diuresis. The dose of the oral diuretic was decreased to 50 mg daily At thi point, he also was taking formula wafers bet een his meals.

By May 13 the patient weight was 198½ pounds. N congestiv changes could be detected on physical examination. H was shifted to hypocaloric, low-sodium breakfast and evening meal,

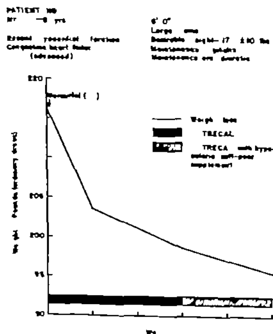


Fig. 2. See text.

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Letter to the Editor

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February 14 1963

T the Editor

The problems in olved n comparison tudies dealing w th the epidemiology of rheumatic fever nd heumatic he rt disease in temperate ersus tropical zones ha been ppropriately nd aptly discussed by Dr Mario R Garcia-Palmieri in the JOURNAL ed orial for November 1962. Differences sampling nd reporting as well as in diagnostic criteria poi t t the need for better designed studies order to determine the incidence and prevalence of these diseases in different geographic areas.

I Hawaii, which is located t 21 degrees north latitude j st south of the Tropic of Cancer no w ll-controlled epidemiological tudies ha e been performed to give conclusi results, but it is the impression of mber of estig tors that rheu matic fever nd rheumatic heart disease occur as often in ma y reas on the mainland of the U ted States I 1941 Doolittle nd Tilden reported cases occurring in the islands nd described clinical manifestations similar t those encou tered elsewhere Tw years later Hartwell and Lam reviewed cases seen in general medical clinic in Honolulu and found 28 patients w th defin t rheumatic al lar disease mong 160 consecutiv cases examined

Further surveys, including hospitalized popula tions inductees, and university tudents, ha estimated he prevalence of rheumatic heart disease in Hawa to be pproximately 2 per cent of the total population [4-7] This latter figure is simila to that found in some survey on the United States mainland and is lower tha that of Framingham Massachusetts where the prevalence has been deter mined t 2 7 per cent of the population between 30 and 59 years of age

Although acute rheumatic fever is reportable disease in Hawa only 5 cases of acute rheumatic fever were recorded in 1961 despit the high incidence during this same period of 481 cases of streptococcal sore throat and 178 cases of scarlet fever Similar figures ha e been reported prior to 1961 Mortality data are incomplete, and it is doubtf l that the low age-adjusted death rate for rheumatic fever and heumatic heart disease (ages 35 t 74), which is about one half of the mainland rate reflects the true incidence and prevalence of these diseases.

The ailable linical data indicate that, as in most temperate limates, the diseases occur most frequently in the younger age groups, nd females are affected slightly more often than males. It is generally agreed that most ttacks of acut rheumatic fever are mild although severe cases are occasionally encountered. After even mild cases, severe valvular disease has been known to occur The valvular predilection is as observed on the United States mainland w th mitral and aortic alves most commonly in ol ed.

The prevalence of rheumatic heart disease is related to eth ic origin since nativ H waiians ha the highest te of all groups li ing on the islands, whereas Japanese ha e the lowest. The reasons for these differences are not clea

Rheumatic heart disease prevention in Hawaii has placed emphasis on a prophylaxis program administered by the Crippled Children Section of the Stat Department of Health nd the Hawaii Heart Association. Approximately 600 children and dult mostly medically indigent are being actively followed by the latter groups, but these represent only fraction of the estimated 12,500 indi iduals with rheumatic heart disease.

The establishment of a rheumatic fever–rheumatic heart disease case registry is being contemplated nd will be designed to provide thorough case finding and follow-up of patients. Hopefully the answers t some of the follow ng epidemiologically mportant questions will be forthcoming (1) What is the true incidence and prevalence of rheumatic fever nd heumatic heart disease in H waii? (2) How does the disease beha e clinically? (3) Do differences exist between the arious islands and geographic localities (4) Are there real differences among the arious thnic groups

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Book reviews

CARDIAC OUTPUT AND REGIONAL BLOOD FLOW. By O. L. Wade, M.A., M.D., M.R.C.P., Professor of Therapeutics and Pharmacology, Queen's University of Belfast, and J. M. Bishop, M.D., M.R.C.P., Reader and First Assistant, Department of Medicine, University of Birmingham. Introduction by K. W. Donald, D.S.C., M.A., M.D., D.Sc., F.R.C.P.E., F.R.C.P., F.R.S.E., Professor of Medicine, University of Edinburgh. Philadelphia, 1962, F. A. Davis Company. 268 pages. Price $9.00.

This is a good and useful book. The measurement of cardiac output and regional circulation in man is reviewed, with most of the emphasis placed on methods utilizing oxygen uptake as the means of approaching estimates of blood flow. New data not previously published are combined with a thorough and critical review of the results of others. Resting cardiac output and the effect of exercise on cardiac output and its regional distribution are considered systematically for each of the common forms of cardiac disease.

The historical development of the important methods is reviewed. The authors point out that "One of the unfortunate effects of the acceptance of the acetylene method in the 1930's was that the dye method which was being developed at that time was discredited.

"One of the interesting results of the introduction of the Fick method was the widespread acknowledgement of the validity of the dye-dilution method ... (p. 33). The authors observe that "Contemplating the criticism Lindhard's work [on the relation of cardiac output and oxygen uptake in man during exercise] has suffered over the years, it is apparent that it is not enough for a scientist's work to be accurate—it must be believed to be accurate" (p. 58).

Not all of the methods or conclusions will be universally accepted. For instance, much of the data on changes in the distribution of cardiac output during leg exercise is based on the assumption that all of the associated increase in oxygen consumption takes place in the legs themselves. In consideration of the nitrous-oxide method for determining coronary blood flow it is suggested that "It seems unlikely that the blood flow to the right ventricle in proportion to its weight will differ greatly from the flow to the left ventricle" (p. 80). It is stated (p. 17) that laminar flow is a necessary assumption for most theoretical derivations ... of the basis of indicator dilution curves.

An ample number of charts summarizing the results are included. There is a bibliography of approximately 700 entries.

This work will be particularly valuable to investigators, although clinical cardiologists will find much that is relevant to their daily problems in the management of patients.

ANNALS OF LIFE INSURANCE MEDICINE 1962, VOLUME I. Edited by the Swiss Reinsurance Company, Zurich, Switzerland. Editorial Committee: Eugene V. Higgins, H. Jecklin, E. Tanner, and Harry E. Ungerleider. Berlin, 1962, Springer-Verlag. 187 pages, 22 illustrations.

This book is composed of seven independent articles which have some bearing on life insurance medicine. The following chapters deserve specific comment.

"The Investigation of Mortality," by H. Wieler is written in a manner which indicates that the author is very competent in this field. He presents an interesting technique for constructing an abridged life table which, he states, is a new approach. Although the material in this chapter is accurate and provocative, it is too technical to be suitable for a doctor of medicine unless he has had considerable technical training. On the other hand, the material is not sufficiently rigorous for actuaries.

The chapter entitled "The Demonstration of Anti-hypertensive Substances in the Urine," by Dr. E. Tanner and associates, of Zurich, Switzerland, describes a laboratory technique which might deserve further research.

The material presented in the following three chapters is well known to life insurance medical directors in the United States and may be of interest to the physician in other fields of medicine. These chapters are "An Appraisal of the Exercise Electrocardiogram Test," by R. S. Gubner, M.D., "The Prognostic Implications of the Electrocardiogram," by H. E. Ungerleider, M.D., and "Cancer—The Challenger," by E. V. Higgins, M.D.

Announcements

THE SECOND INTERNATIONAL CONFERENCE ON CONGENITAL MALFORMATIONS, sponsored by The National Foundation-March of Dimes and organized by the International Medical Congress, Ltd., is to be held at the Americana Hotel, New York City, on July 15-19, 1963. Registration and the pre-conference reception will take place on July 14.

The Conference Secretary is Stanley E. Henwood, 120 Broadway, New York 5, N. Y. In charge of press arrangements is Charles Bennett, Science Information Division, The National Foundation, 600 Second Ave., New York 17, N. Y.

FELLOW IN CARDIOVASCULAR ROENTGENOLOGY RESEARCH. Stipend of $6,500 a year; provisions for equipment and facilities of $5,000. Master's degree and Ph.D. program available in the graduate school. The candidate should have completed the equivalent of 3 years of training in roentgenology.

Make application to Dr. B. J. O'Loughlin, Department of Radiology, U.C.L.A. Medical Center, Los Angeles 24, Calif.

THE 16TH ANNUAL CONFERENCE ON ENGINEERING IN MEDICINE AND BIOLOGY will be held in Baltimore, Maryland, at the Lord Baltimore Hotel, Nov. 18-20, 1963. The Conference is sponsored jointly by the Institute of Electrical and Electronics Engineers and the Instrument Society of America.

Chairman of the Conference is George N. Webb and the Secretary is Richard E. Rogers, both of Johns Hopkins University, Baltimore. Dr. Robert L. Schoenfeld of Rockefeller Institute, New York, is program chairman. Dr. David Robinson of Johns Hopkins, is digest chairman. Guy Knickerbocker of John Hopkins, is discussion group chairman. Everett E. Smith of Minneapolis-Honeywell Regulator Company, is publicity chairman. Edmund Glaser of the University of Maryland Medical School, is scientific exhibit chairman and Martin Whitcomb of Whitcomb Associates, is local arrangements chairman.

A nine-month TUTORIAL PROGRAM IN CARDIOLOGY from Sept. 15, 1963 to June 15, 1964 will be offered by the Institute for Cardiopulmonary Diseases, Scripps Clinic and Research Foundation, La Jolla, California.

This will be an intensive, academic effort covering the field of cardiovascular diseases and is especially designed for the practicing physician who desires thorough instruction in this field and for the physician who is finishing his period of formal training and wants a final intensive orientation in cardiology.

For details, write: Executive Secretary, Institute for Cardiopulmonary Diseases, Scripps Clinic and Research Foundation, La Jolla, California.

The Annual Meeting of the AMERICAN ACADEMY OF PHYSICAL MEDICINE AND REHABILITATION will be held at the Sheraton-Dallas Hotel, Dallas, Tex., on August 26, 1963.

Direct all communications in regard to this meeting to M. K. Newman, M.D., 16661 Wyoming Ave., Detroit 21, Mich.

The American Board of Pediatrics announces that the WRITTEN EXAMINATIONS of the SUB-BOARD OF PEDIATRIC ALLERGY and of the SUB-BOARD OF PEDIATRIC CARDIOLOGY will be held on June 21, 1963.

The closing date for the receipt of applications from those candidates who wish to take this written examination is May 10, 1963.

The oral examinations in each specialty will be held in October, 1963, the exact dates for which will be announced later.

The Leukemia Society, Inc., announces a program of FIVE-YEAR SUPPORT FOR CAREER INVESTIGATORS IN LEUKEMIA RESEARCH. $15,000 per annum is to be awarded for 5 years, renewable to 10 years, to qualified investigators in basic science or clinical departments of medical schools, universities, and research institutes.

The Leukemia Society Scholar, whose research is broadly related to the problem of leukemia, is expected to serve as a regular member of the faculty or staff of his institution.

Nominations should be submitted no later than March 15 or October 15 to the Medical Director, Leukemia Society, Inc., 211 East 43rd St., New York 17, N. Y. All material should be submitted in six copies, and include a small photograph.

The Fifteenth Annual Meeting of THE SOCIETY FOR CLINICAL AND EXPERIMENTAL HYPNOSIS will be held October 23-26, 1963, at the Barbizon Plaza Hotel, New York City.

Address correspondence to: George Wallace, M.D., Arrangements Chairman, 9101 Shore Road, Brooklyn 9, New York.

The Annual Meeting of the AMERICAN ASSOCIATION OF ELECTROMYOGRAPHY AND ELECTRODIAGNOSIS will be held on August 25, 1963 at the Sheraton-Dallas Hotel, Dallas, Tex.

Address all communications in regard to this meeting to M. K. Newman, M.D., Director of Public Relations, 16661 Wyoming Ave., Detroit 21, Mich.

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Editorial

The syndrome of proteinuria
The nephrotic syndrome

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The functional pathology of the nephrotic syndrome is the glomerular leakage of albumin which results in a low level of plasma albumin with consequent reduction of the plasma osmotic pressure and hypovolemia. Hypotonic hypovolemia promotes antidiuresis and antinatriuresis (presumably by increased vasopressic and aldosteronic activity) which in a vain effort to expand the plasma volume expands instead the extravascular extracellular fluid to increase edema.

The sterile argument decrying the use of the euphonic noun nephrosis coined by Muller[1] then illogically converting it to the dysphonic polysyllabic nephrotic syndrome drags wearily on. The fact is that neither nephrosis nephrotic syndrome tubular nephritis[2] lipoid nephrosis lipemic nephrosis[3] the edematous syndrome of nephritis, Type II nephritis nor any other name is universally acceptable, however frequently enterated. Each investigator must choose and define his own terminology.

The clinical syndrome under consideration may be arbitrarily defined as one in which gross proteinuria principally albuminuria and related hypoalbuminemia are always present edema and hyperlipemia are often present and hypogammaglobulinemia systemic hypertension azotemia and excessive erythrocyturia are sometimes present. Aptly described as the protein losing kidney by Platt this condition has many names and more causes than names the incriminating etiological factors exceed a score and vary from sarcoma to snake bite. A simple arbitrary classification system is given in Table I it is not intended to be comprehensive.

This nonspecific yet remarkably typical clinical syndrome stems from the basic theme of gross proteinuria upon which age sex primary cause and response to treatment do but superimpose variations. It is no more difficult to accept renal edema as caused by one or more of a multiplicity of factors producing proteinuria than it is to accept cardiac edema as due to many mechanisms with a common terminal pattern.

The narrower field of idiopathic nephrosis with or without concomitant glomerulitis is the subject of present discus-

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Table I. The nephrotic syndrome (the syndrome of proteinuria)

A. *Congenital N phrosis.* A group of conditions resulting in persisting gross proteinuria in young infant who are siblings. The disease ma be severe nd rapidly lethal, with a closely similar pattern in each sibling, or may ry widely in severity and duration in different members of the same family. The condition is certainly congenital although not alw y patent at birth and may be hereditary due to isoimmunity or to damage ed by aternal antibodies transmitted antenatally to the fetus

B. *Sec ndary N phrosis*

(1) Collagen nephrosis. Anaphylactoid purpura, disseminated l pus erythematosus, polyarteritis nodosa

(2) Postnephritic nephrosis. A rare sequel t acute hemorrhagic glomerular nephritis

(3) Renal ei thrombosis

(4) Diabetic glomerulosclerosis

(5) Toxic nephrosis due to

( ) Hea y metals, such as lead nd mercury

(b) Drugs, such as Tridione

( ) En enomation by snake bit

(6) Allergic nephrosis. Following nhalation of pollen, bee stings, or immunizing injections, such as poliom elitis vaccine

(7) Amyloidosis

(8) Diverse rare causes. Sarcomatous infiltration

C. *Idiopathic N phrosis.* This condition account for the great bulk of the cases which occur in hildhood and small proportion of cases in adult life. It occurs with no obvious precipitating or underlying cause. Tw types are readily distinguished

(1) Those with concomitant glomerulitis as evidenced by excessi erythrocyturia, and/or azotemia, nd/or systemic hypertension

(2) Those without concomitant glomerulitis. Judged by bsence of the bove-mentioned criteria

sion. It will be considered under the headings of etiology, natural history, prognosis and treatment.

Etiology

Absolutely the etiology is not known and views on pathogenesis vary widely. The basic divergence of thought depends on whether glomerular damage is due to autoimmu ization and the development of antihuman kidney antibodies or to antibodies primarily antagonistic to exogenous antigens (such as viral or bacterial invaders) directly and coincidentally damaging glomeruli or indirectly implicat ng the glomeruli in the immunologic consequences of attacking the primary agent localized therein. Whichever view prevails, the scientist must view with admiration the Herculean labors of Heymann and his co-workers during the past decade. However relevant or otherwise such experimental animal studies may eventually prove to be they have added greatly to our knowledge of the histopathology of the nephron under assault by heterologous antibodies, homologous antibodies, and autologous antibodies. These and other studies clearly indicate that a wide variety of cytologic glomerular patterns may result from the use of the same antibody under differing experimental condition with damage to the pedicels a constant undertone.

The pleomorphic histology of such affected glomeruli admonish one to treat with proper reserve results derived from renal biopsy by acupuncture based on a small proportion of glomeruli at one given point in time. Such assessment is best treated as speculative considered with interest and reviewed critically when the natural history of the individual case unfolds. The clear variations in the pattern of the lesion in avian and mammalian species in the laboratory demand caution in translating results to man in his natural environment.

Nevertheless the application of electron microscopy coupled to percutaneous renal biopsy pioneered most effectively in Cuba by Galan has led to accurate definition of the anatomic changes associated with the syndrome of proteinuria. When glomerulitis is present as reflected by systemic hypertension, azotemia or excessive erythrocyturia histologic change is apparent on light microscopy. The changes are in the nature of a n embranous glomerulitis with thickening of the epithelial basement mem

brane. When light microscopy fails to reveal abnormality electron microscopy will usually do so.[1] It would seem that whatever the etiology the functional defect of gross proteinuria is reflected in abnormality of the podal processes (pedicels) of the epithelial layer of the basement membrane of the glomeruli Litman[13] demonstrated how difficult it is to predict the outcome when the glomerular changes found on renal biopsy are minor When changes are gross, the outcome has usually been in little doubt before biopsy Percutaneous needle biopsy carries many hazards, including loss of life or a kidney or peritonitis and not the least of which is the reaction of an observer who places too great faith on too few glomeruli! Although the technique occasionally reveals the primary causes of secondary nephrosis due to diseases such as disseminated lupus erythematosus, t has proved of little value to the individual patient with primary nephrosis. Whether the information gleaned from serial biopsy of kidneys during various stages of the disease will eventually yield practical as well as academic dividends is problematical.

Natural history

Long term studies of idiopathic nephrosis in childhood by Hooft and Eeckels[13] Todd Lawson and associates[14] and Blainey and associates have confirmed that the ultimate prognosis is better than was formerly believed. Provided that the patient does not present with complicating glomerulitis (i.e. excessive erythrocyturia ± systemic hypertension ± azotemia) and does not succumb to acute infection during the first year of the disease the natural tendency is to recovery It should be stressed that this was so before steroid therapy became available

The characteristic and distressing edema with its wild fluctuations and dramatic impact have fascinated clinicians for generations past In modern times the classic studies of Metcoff and Janeway in this respect merit close attention In the past undue concentration on relieving the edema by dramatic diuresis did much to obscure the vital importance of eliminating the underlying proteinuria on which the ultimate outcome depended Assessment of prognosis has been difficult in the past because so many retrospective reviews failed to trace sufficient of the cases for long enough and were significantly incomplete A recent survey of 164 children from Glasgow Scotland at least had the merit of completeness and the results in regard to outcome are shown in Table II which compares the findings with the survey of 161 cases in Boston U.S.A. (Barness and associates) Such results retrospective in type and localized in character are probably valid in detail for one region only but the similarity in results is interesting

Misconceptions in regard to the outcome of the disease are legion These are usually based on impressions gleaned from a small number of cases, biased by local conditions and by the age groups of patients admitted to specific units and bedeviled by incomplete follow-up. The latter was particularly true of the large group published by Barnett and associates,[18] in which a number of incompletely supervised groups from different geographical regions were amalgamated to give the largest total of cases then recorded. Weight of numbers can never replace complete and accurate following of cases preferably by a small number of observers.

The common pattern of idiopathic nephrosis is recovery within 2 years. Recovery may occur after a longer period otherwise the downward course of the disease falls into three types. During the first 2 years

*Table II Natural history of idiopathic nephrosis**

Ultimate outcome of the illness	*Scotland (Glasgow) 1929-1957*	*U.S.A. (Boston) 1924-1946*
Total cases	164	161
Number traced	164 (100%)	136 (85%)
Number followed for 2 years	164 (100%)	107 (67%)
Asymptomatic and no proteinuria	80 (49%)	44 (41%)
Dead	62 (38%)	45 (42%)
Alive	102 (62%)	62 (58%)

*In each of these series, most deaths were due to infection prior to effective antibiotics becoming available. The steroid diminution of this hazard should reduce the mortality to ap[illegible]ely 30 per cent.

after onset the gross edema underlying wasting and low levels of gamma globulin prevailing predispose to infection by various streptococci such as pneumococci. In recent years the use of antibiotics, effective diuretics, and the effects of steroid therapy in arresting proteinuria, raising the levels of plasma albumin and gamma globulin and promoting tissue anabolism have largely *eliminated such deaths.* In the series quoted above deaths due to infection were responsible for 75 per cent of the mortality during the first 2 years after onset of the disease and for 58 per cent of the total mortality recorded. The second type of death is progressive renal failure. Among our cases 30 children (18 per cent) died of this at periods which varied from 1 to 10 years after the onset of the illness. It is difficult to draw irrefutable conclusions that the figure has been reduced by prednisolone therapy since 1955. Thirdly, a small group of patients (4 per cent) continue with proteinuria but no other signs of the illness for more than 10 years. Renal function appears to be adequate and one wonders whether this might not continue indefinitely.

The interpolation of effective steroid therapy and effective diuretics have altered the natural history of the disease beyond recognition. The usual pattern now is for the patient to become edematous, thereafter to be treated by steroids and or diuretics and either rendered asymptomatic without proteinuria or asymptomatic with proteinuria. *In either event relapses* are common proteinuria increasing and edema returning. This intermission of improvement and relapse exaggerates the similar natural pattern of the disease but raises many problems relating to the cause of relapse and as to whether an asymptomatic patient with proteinuria requires further steroid therapy.

Treatment

The four forms of treatment commonly employed today are (a) dietetic (b) steroid (c) diuretic and (d) antibiotic. Each of *these will now be considered briefly.*

Dietetic treatment. The daily loss of sodium in the urine may be as low as 10 mg in the nephrotic syndrome and restriction of the daily intake of sodium to 250 to 1 000 mg may slow the rate of formation of edema but will rarely provoke diuresis. Restriction of the intake of water is of no practical value. When urea clearance is satisfactory and a patient is to commence massive steroid therapy his habitual daily intake of calories should be assessed and an isocaloric diet rich in protein and low in sodium content prescribed. In this way the development of Cushingoid obesity may be slowed. There is no indication for the restriction of protein in the absence of azotemia since the rounded contours of nephrotic edema frequently mask the wasted and protein-depleted tissue underlying. Blainey[21] has shown the potential benefits of protein rich diets to the chronically ill adult patient. Only when terminal renal failure ensues is moderate restriction of protein indicated.

Steroid therapy. When nephrosis is of the idiopathic type and uncomplicated by glomerulitis, as evidenced by hematuria hypertension or azotemia the use of corticosteroid therapy is strongly indicated. Since 1955 prednisolone[22] and more recent steroids have been given in intensive continuous dosage by many European investigators. This superseded the use of corticotrophin and cortisone. In some centers, initial intramuscular corticotrophin treatment followed by cortisone given intermittently and rather mystically on certain days of the week but not on others was the vogue until recently.[23,24] What becomes increasingly clear is that no system of *dosage has any significant advantage over* other forms and probably all best results depend on the familiarity of the clinician with the treatment employed and the disease being treated. Basically one employs the dose of steroid necessary to suppress abnormal proteinuria and to maintain this state. The steroid should have the least sodium-retaining effect and range of side effects compatible with achieving these ends. In our experience prednisolone is the most effective steroid with relatively fewer side effects than cortisone, hydrocortisone corticotrophin dexamethasone, *or triamcinolone. The recent indication* of differential efficacy resulting in successful triamcinolone treatment of nephrotic patients nonresponsive to prednisolone therapy (Lorber[25]) merits study but here tri

amcinolone was discarded because of too frequent severe side effects.

The dosage presently employed at the Royal Hospital for Sick Children Glasgow is as follows.

ORAL PREDNISOLONE THERAPY The initial dosage of prednisolone is 60 mg daily for 10 days, then 40 mg daily for 10 days and 20 mg daily for 10 days. If proteinuria approaches normal levels (i.e. 250 to 100 mg daily) the dosage of steroid is then slowly reduced and omitted over a period of 20 to 120 days. This titration of steroid dosage against proteinuria is reflected by temporarily stepping up the dose level if proteinuria relapses to a gross state.

Little Cushingoid change will result from 40 days of treatment provided that proper dietetic supervision of a low sodium isocaloric protein-rich diet is carried out. Side effects, aside from obesity are unusual in children during the initial steroid course but initial azotemia or hypertension may be aggravated. Convulsions, hypokalemia, mental deterioration and paresis can occur.

The main problems of steroid therapy today seem to be (1) how to avoid relapses of proteinuria (2) when to withhold steroid therapy on account of hematuria azotemia or hypertension in a variety of combinations and (3) when to give up hope of successful steroid therapy when proteinuria persists with or without edema.

The problem of preventing relapses is largely unsolved. Relapses may occur after years of normal proteinuria and these cannot be predicted except in so far as they are not infrequently heralded by viral respiratory infection. Certainly neither antibiotic prophylaxis with or without continuous or intermittent steroid therapy is absolutely preventative.

The final benefits of steroid therapy are not clear. Idiopathic nephrosis in children probably ends in complete recovery in at least 60 per cent of the cases if intercurrent death from infection is prevented even *without* steroid therapy. This trend is indicated in Table III which covers the period 1929 1957.

This efficacious treatment is not without its price if prolonged or repeated courses of steroid are given. The typical changing face of nephrosis is illustrated when periorbital edema yields to diuresis only to be replaced by tomato-face (moonface). Prolonged steroid therapy may produce dwarfism which fortunately is potentially reversible. Cutaneous striae occur more frequently with triamcinolone and dexamethasone than with prednisolone. The dreaded complication of convulsions with or without hypertension or hypokalemia may lead to psychopathic changes or to permanent neurological damage such as hemiparesis.

It has been shown repeatedly that in most instances steroid therapy shortens the period of gross proteinuria and edema returns the levels of plasma albumin and gamma globulins to normal and improves the nutrition of the patient. All of these facts in combination with antibiotic therapy have largely eliminated the mortality from acute infection during the first 2 years of the illness which formerly accounted for approximately one half of the total mortality. It is less certain but probable that deaths from uremia during the first 4 years after the onset of the disease have been reduced. The eventual effects of steroid on death from renal failure are yet to be determined.

The side effects of steroid therapy such as tomato-face buffalo-hump cutaneous striae, and obesity are reduced by efficient dietetic supervision. Transient glycosuria is common and harmless. Hypertensive crises, hypokalemia, and convulsions usually occur when repeated courses are given or when patients with initial hypertension or impaired renal function are treated without adequate monitoring of the blood pressure and the homeostatic state.

Diuretic therapy Diuretic therapy is usually unnecessary for steroid-responsive patients and is employed when steroid therapy is unsuccessful or when the patient is considered to be unsuitable. The forms of diuretic therapy employed during the past 50 years have been legion. Urea, citrates mercurial compounds, cation exchange resins, plasma substitutes, human plasma blood and albumin and many others have all been tried found wanting and abandoned. This is not surprising since they do not check the basic proteinuria and only expand plasma volume temporarily. Steroid treatment alone will still arrest proteinuria.

Treatment today largely resolves into attempts to interfere with the fantasticall

*Table III Improving prognosis of idiopathic nephrosis 1929 1957**

	Number of cases	Alive (%)	Dead (%)	Asymptomatic (%)	Proteinuric (%)
1929-1936 Pre-sulfonamide	11	64	36	28	36
1937 1945 Sulfonamide	41	66	34	32	34
1946-1950 + Penicillin	37	62	38	48	14
1951 1955 + Cortisone	53	81	19	42	39
1955-1957 + Prednisolone	22	91	9	64	27
1929-1957 Total	164	73	27	43	30

[illegible]

efficient reabsorption of sodium by the renal tubules Two main types of diuretic are of use namely the thiazide groups (chlorothiazide hydrochlorothiazide etc.) which act mainly on the more important proximal tubular absorption and aldosterone antagonists such as spironolactone, which block the less quantitative sodium retention of the adrenal hormone The importance of aldosterone retention of sodium has probably been exaggerated and undue emphasis placed on uncritical estimates of the significance of secondary aldosteronism in nephrotic edema. Proximal tubular handling of sodium and water is more likely to be the key to the problem

It is not difficult to render a patient free of edema by restriction of sodium supplementation of potassium and effective thiazide treatment with antialdosterone complementation It is difficult to leave such a patient on prolonged palliative treatment without feeling impelled to essay another attack on the persisting proteinuria. It is prudent to *keep the patient on maintenance diuretic treatment while* testing the effect of steroid If the steroid treatment succeeds the diuretics may be discontinued if the steroid therapy fails the increase in edema will be mitigated if not prevented

The danger of hypokalosis only arises when the supplementation of potassium has been inadequate. The dose of potassium chloride suggested below should be adequate but daily output of urinary potassium may be monitored and occasional plasma concentrations measured

SCHEME OF DIURETIC TREATMENT (1) *Diet* to contain less than 1 Gm of sodium daily (2) *Supplementary potassium* 1 to 4 Gm. daily (i.e. 2 to 8 Gm of KCl) depending on the content of potassium in the urine. (3) *Chlorothiazide,* 2 to 8 Gm daily (or equivalent dosage) for 1 week and then add (4) *Spironolactone* 200 to 400 mg daily This synergistic combined treatment may be continued indefinitely

Antibiotic therapy Antibiotic therapy may be therapeutic or prophylactic Such therapy should never be withheld when acute infection arises since the most likely result is death diuresis is not common and relapse is usual There is no need for prophylactic therapy if a patient is on steroid therapy nor is prophylactic antibiotic therapy of proved value in preventing relapse. The edematous patient is most liable to streptococcal infections such as those due to Pneumococcus, and penicillin is the therapy of choice During the period of gross edema malnutrition and hypogammaglobulinemia antibiotic treatment should be vigorous and unrestricted

It may be true that steroid therapy masks acute infection in patients but such occurrences usually deceive only inefficient supervision and is not such a likely hazard in an efficient unit as to merit concomitant prophylactic antibiotic therapy

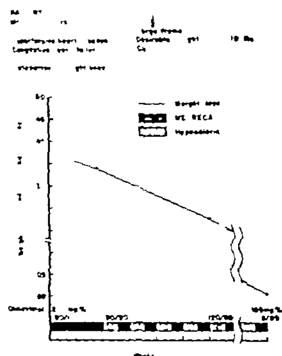


Fig. 3. See text.

but was advised to continue taking formula for lunch and at bedtime. By June 1 his weight had further decreased to 195½ pounds—a total loss of about 21 pounds in 38 days. The dose of hydrochlorothiazide thereafter was reduced to 50 mg. 5 days a week without incident.

Case 3. Successful treatment of both congestive failure and marked obesity digitalis withheld (Fig. 3). P. B., a 53-year-old rotabler presented himself on Aug. 13, 1959 with hemoptysis persistent crepitant rales throughout both lower lung fields and slight pitting edema of the lower limbs. He was known to be hypertensive. Previous bronchoscopy and bronchographic study had failed to disclose any abnormalities. The patient initially weighed 249 pounds. His height was 5 feet 11½ inches. He had a large body frame. Notwithstanding that he was instructed concerning a prescribed hypocaloric diet, his weight had declined to only 247 pounds 2 weeks later.

The patient was then placed on a diet that consisted of four glasses of formula daily supplemented by lettuce and tomatoes as desired. He also was given a single injection of a mercurial diuretic. Digitalis was withheld. By September 1 he weighed 236 pounds—a decrease of 11 pounds in 5 days. By September 9 his weight had declined to 234½ pounds. His blood pressure had decreased in a stepwise fashion from initial readings that averaged 180/110 to 130/90 mm. Hg. In addition to the cessation of hemoptysis and pulmonary congestion, his right knee—which previously had caused him sufficient difficulty to require intra-articular injections of hydrocortisone by an orthopedic surgeon—was strikingly improved. (This was a rather important consideration for this patient because of the nature of his work.)

Thereafter the patient alternated 3 days of formula with 4 days of a standard 1,200 calorie diet. On October 6 his weight was 222¾ pounds. By continuing the above-mentioned regimen his weight progressively declined to 210 pounds on November 10 and to 200½ pounds on December 8, 1959. His blood cholesterol concomitantly decreased from an initial value of 243 mg. per cent to 222 mg. per cent on October 6 and 188 mg. per cent on December 8. During this entire period the patient had continued his work without interruption or significant fatigue.

Case 4. Successful management of congestive failure complicating a recent myocardial infarction, digitalis withheld (Fig. 4). F. K., a 62-year-old retired white man, had been treated several months previously for an acute myocardial infarction. During this illness persistent bibasilar râles were found for which he was placed on hydrochlorothiazide (25 mg. daily) and advised to abstain from salt. He also had been given the anticoagulant Liquamar.

Because of his subsequent progressive increase in weight, associated cough and evidence of recurrent pulmonary congestion when seen on May 25, 1961, he was given a single injection of a mercurial diuretic. He also was advised to increase the dose of hydrochlorothiazide to 50 mg. daily and to take four glasses of formula a day as his sole source of calories. On that date, he weighed 207½ pounds. He was 6 feet tall and had a large body frame. By May 29 his weight had declined to 201¾ pounds. The patient's subjective improvement was corroborated by a decrease in discernible pulmonary congestive changes.

He was then continued on a standard low-sodium breakfast with formula liquid or pudding for his other meals and at bedtime. By June 13 his weight had decreased to 193½ pounds. Râles no longer

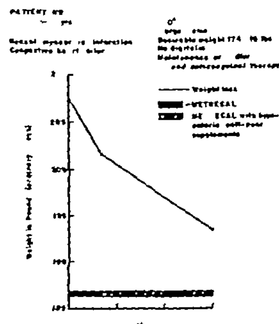


Fig. 4. See text.

Prognosis

In 1904 Maillard[1] made it clear that the prognosis of the nephrotic syndrome was much better in children than in adults It seems likely that this is due principally to the very much higher relative incidence of secondary nephrosis in the adult age group and secondarily to the reaction of the adult kidney and vascular system which is different from that in the child. The merit of the low-salt diet was by then appreciated

Prognosis in children can be estimated from a number of factors

1 Age. The outlook deteriorates with age the optimal prognosis being when onset begins between the sixth and thirty-sixth months of age when the recovery rate was 70 per cent

Presence of glomerulitis The presence of excessive erythrocyturia and/or hypertension and/or azotemia are all bad prognostic signs. For those with such signs the death rate was around 62 per cent for those without glomerulitis it was around 33 per cent.

3 Sex The prognosis for life is better in girls (71 per cent) than in boys (57 per cent) although more girls (19 per cent) than boys (10 per cent) continue to have chronic proteinuria.

4 Duration of edema and proteinuria. Prolongation of episodes of edema or gross proteinuria are bad prognostic signs The death rate for children with edema of less than 3 months duration was 25 per cent and for the remainder it was 46 per cent.

After these observations have been made t is still true that idiopathic nephrosis is a capricious and largely unpredictable condition The long term follow-up of cases in recent surveys spotlighted the difficulty in predicting th outline.

It has been made clear that percutaneous or more adequate forms of renal biopsy may indicate histologic changes of the glomerular basement membrane which are suggestive of a less good prognosis. In idiopathic nephrosis with doubtful glomerulitis it is questionable whether such findings are sufficiently definitive early in the disease to be dependable and when gross glomerulitis is present biopsy offers little prospect of improving the outlook for the patient. Congenital nephrosis is lethal at an early age and the prognosis in these cases is not a statistical problem since we have little but symptomatic treatment to offer In any form of secondary nephrosis in which the underlying condition cannot be cured the prognosis is bad In the adult with secondary nephrosis due to glomerulosclerosis, amyloidosis or lupus erythematosus the future depends on the basic lesion When recurrence of an acute incident be it snake bite or renal vein thrombosis, can be avoided the outlook is good To the young child with primary nephrosis and no glomerulitis the era of steroids and antibiotics can offer a likelihood of recovery in 75 per cent of the cases.

The difficult groups to predict are the adult patients with primary nephrosis, and patients with primary nephrosis with glomerulitis at any age. Although the outlook for duration of life cannot approach normality yet proper diet and appropriate diuretics are palliative therapies at hand The hazard of infection is held in check by antibiotics and one essays steroid therapy in hope if not in expectation unless primary disease hypertension azotemia or previous reaction to steroid preclude this.

The outlook is therefore good in parts. The pessimism of former years based on observation of chronic brine logged infection-ridden invalids is no longer justifiable. If we know the complete answer to nothing there is yet nothing to which there is no partial answer and a more pleasant longer life awaits the modern victim of this mysterious and fascinating condition than was in store for his like a generation before

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Clinical communications

Artificial pacemaker for treatment of Adams-Stokes syndrome and slow heart rate

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Myocardial excitation can easily be performed by electrical stimulation. However, because of several technical problems involved, electrical cardiac pacemaking has not been adapted as a therapeutic procedure until recent years.

In 1952 Zoll[1] and associates published their first report of closed-chest cardiac stimulation in man. For long-term treatment the application of electrodes directly to the myocardium is more advantageous, and in recent years several groups of workers have presented accounts of various methods.[2-11] Surveys of the problems of cardiac pacemaking have been published by Bellet,[12] Zoll and Linenthal,[13] and Stephenson.[14]

The present report includes a description of a procedure for continuous cardiac pacemaking by myocardial electrodes, and an account of 18 consecutive patients who were treated by this method. In addition, some of the problems in regard to the choice of a suitable rate and intensity of stimulation are discussed.

Methods

Technical description of apparatus. Two types of pacemakers will be described. One is carried by the patient outside the body and requires percutaneous leads to the myocardial electrodes (Figs. 1 and 4). Since the other ends of the leads are accessible, threshold values for effective cardiac stimulation can be measured. Partly on the basis of the results hereby obtained an implantable pacemaker (Figs. 2 and 3) has been constructed.

1. PACEMAKERS.†

Pacemaker for external use. The impulse generator is a blocking-oscillator which gives pulses of 2.5-msec. duration to a switch transistor. The latter allows discharging of a 4.7 μf condenser between the electrodes. The condenser is charged by a battery which consists of 9 mercury cells. Because of the condenser coupling the net flow of current between the electrodes will be zero.

By a step switch the impulse amplitude can be varied between 2 and 11 volts, and

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†The external pacemaker is designated EM 130 and the implantable pacemaker, EM 137. Both are manufactured by Elema-Schönander Corporation, Stockholm, Sweden.

similarly the frequency is variable between 5 and 110 impulses per minute The rate of stimulation is independent of the resistance in the outer circuit

The battery is interchangeable With intermediate frequency and amplitude it has an expected lifetime of 1½ years.* If maximum rate and impulse strength are employed the lifetime will be reduced to 9 months

Pacemaker for implantation Basically the electronic construction of this apparatus is the same as the one described above but the frequency is fixed at about 3 impulses per minute and the voltage is set at approximately 6 5 volts. The battery contains 5 mercury cells. Because of the low consumption of current (approximately 50 microamperes) the lifetime of the battery is more than 2 years. The assembled electronic components are embedded in epoxy resin which thereby constitutes the outer surface of the pacemaker Two screw connections for the electrode cables are covered by a plastic screw. The connections between pacemaker and cables are further sealed by silicone grease to prevent entrance of body fluids.

2 ELECTRODES The myocardial electrode is a round disc of pure platinum with a diameter of 9 mm It is applied directly to the epicardial surface of the heart and has two holes for suturing The back of the electrode is insulated with a rounded off layer of epoxy resin

For stimulation two such electrodes are used one initiates the excitation of the myocardium and the other functions as an indifferent electrode

3 CONNECTING LEADS. Each myocardial electrode is attached to a lead which consists of four very thin bands of stainless steel wound upon a core of spun Terylene The lead is insulated with polyethylene The cable thus obtained is exceptionally flexible and durable Special tests, performed at the Royal Institute of Technology (KTH) in Stockholm have shown that its lifetime can be expected to be practically unlimited

Surgical procedure By an anterior subcostal thoracotomy under the sixth left rib and an incision of the pericardium parallel to the phrenic nerve the anterior wall of the heart is exposed. The electrodes are sutured with 0-0 Deknatel silk to such areas of the epicardium as are free from epicardial fat. The requirements of stimulus strength do not differ whether the right or the left ventricle is used for stimulation nor has any apparent difference in hemodynamic results been noted For theoretical reasons, initiation of the excitation at the apical part of the heart has been considered to imitate the normal spreading of the excitation wave most closely and therefore placing of the electrodes on the apical part of the heart wall is aimed at. One or two additional electrodes are applied as reserves, and the respective cables are drawn subcutaneously to the epigastrium where the ends are left under the skin

When an external pacemaker is to be used, the leads of the stimulating electrodes are drawn through an intact intercostal space and down to the region above the left groin where they are taken out through the skin and connected to the pacemaker The purpose of this long subcutaneous route is to minimize the risk of infection along the cables.

The implantable pacemaker is placed in the abdominal wall the rectus abdominis muscle sheath has been found to constitute a suitable place and the pacemaker is placed at the posterior aspect of the muscle. When the battery is expected to run down (after about 2 years) the pacemaker has to be replaced by a new one which will be connected to the same leads. This is a simple procedure and the operation might be done using local anesthesia.

Measurement of stimulus threshold and impedance If the electrode leads are accessible as in the patients supplied with external pacemakers, threshold values for myocardial excitation can easily be determined. For such measurements an impulse generator giving an impulse of the same type as that of the pacemakers described but with continuously variable output voltage is used Voltage and current are visualized on the screen of an oscilloscope. Because the impulse is obtained by a condenser discharge and the circuit of a patient and pacemaker includes

*The lifetime of batteries is estimated on the basis of ratings given by the manufacturer Mallory Batteries, Ltd., Dagenham, Essex, England.



Fig. 1. Pacemaker for external use (EM 138). The frequency and amplitude controls can be operated by screw driver or by small coin. The Plexiglas adapter is connected to the distal ends of the electrode leads. The pacemaker measures 10.5 by 7.5 by 3.5 cm. It has weight of approximately 400 grams.



Fig. 2. Pacemaker for implantation (EM 137) with leads and myocardial electrodes connected. The pacemaker measures 6 cm. in diameter and is 2.2 cm. thick. It has a weight of 170 grams.

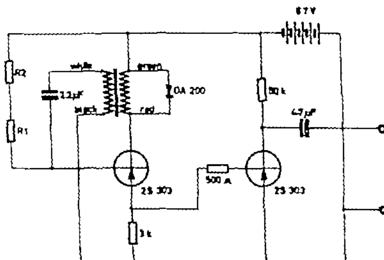


Fig. 3. Circuit diagram of the implantable pacemaker. The external pacemaker has similar construction, but (1) impulse amplitude can be varied by altering the number of mercury cells actually connected and (2) variation of frequency is achieved by substitution of resistance *R1* by variable resistance managed by step switch.



Fig. 4. External pacemaker carried by a patient in special pocket with belt and shoulder band.

both capacitive and resistive elements the time-course of voltage and current will both show a logarithmic fall (as shown in Fig. 5).

Initial impedance is peak voltage divided by peak current.

Stimulation threshold is defined as the minimal impulse that is capable of myocardial excitation during diastole. For threshold determination a stimulus rate of 50 to 0 impulses per minute has been used. The efficiency of the stimulation is controlled by simultaneous recording of the electrocardiogram.

Clinical material

Clinical data on the 18 patients have been summarized in Table I. Disturbances in rhythm and conduction dominated the symptoms of all the patients. Slight congestive heart failure apparently unrelated to the heart block was present in one patient (Case 3) and valvular disease in one (Case 9). No patient presented a typical history of angina pectoris or myocardial infarction. Adams-Stokes attacks had occurred at some stage of the disease in all patients, but Cases 3, 10, 15, 16 and 18 at the time of operation had been free from attacks for several months. The electrocardiogram had been registered during one or more attacks in 15 patients; 13 had shown ventricular asystole as the cause of circulatory arrest. In Cases 5 and 17 paroxysmal ventricular tachyarrhythmia (flutter fibrillation) had been recorded. Prior to operation the majority of patients underwent a thorough cardiological investigation which also included therapeutic trials of various antiarrhythmic drugs.

About half of the patients were more than 60 years old and it is reasonable to consider coronary disease as a possible cause of the conduction disturbance. In the absence of reliable evidence for ischemic heart disease or other myocardial disease in most of the patients, we have refrained from an etiological grouping.

The main indication(s) for operation in each case is (are) given in Table I according to the following classification: (1) Chronic forms of Adams-Stokes syndrome. In this group the recurring attacks of syncope and the disabling somatic and psychological consequences form the dominant problem. (2) Acute disease states characterized by varying degrees of A-V block, periods of extremely slow heart rate and frequent severe Adams-Stokes attacks (whether caused by asystole or ventricular tachyarrhythmia). The danger of fatal outcome constitutes the predominant factor in clinical assessment. (3) Conditions dominated by a slow fixed—or almost fixed—heart rate, usually due to complete heart block. The resulting inability to increase cardiac output imposes a pronounced physical handicap.

Although this classification is somewhat artificial it has been a useful basis for the discussion of operation since each category presents different problems in regard to clinical assessment and evaluation of prognosis.

Approximately half of the patients had a supraventricular rhythm (usually first degree A-V block) at the time of operation. Such a rhythm has not been considered to be a contraindication to artificial pacemaking (cf. Figs. 8 and 9).

Results

Of the 18 patients, 16 are still alive. One patient (Case 13) died 8 days postoper

atively from ventricular fibrillation probably unrelated to pacemaking (see below) The other death (Case 17) occurred during operation The myocardium was excessively fragile and suturing resulted in multiple rifts which could not be adequately repaired. At autopsy microscopic examination revealed a recent myocardial infarction estimated to have occurred about 12 hours before death No symptoms had been reported by the patient. The electrocardiogram (Lead I) was continuously recorded during operation but did not show any change suggestive of infarction.

Those patients who had constant complete heart block before operation reported a considerable increase in physical fitness after the pulse rate had been artificially increased. An improved physical working capacity has also been possible to determine objectively (These matters are being studied further)

Eight patients at the time of operation were less than 60 years old Except for one who died all have been able to return to active work. Three male patients with complete heart block had been unable to work for from several months to 4 years because of severely reduced physical working capacity They have returned to their previous occupations as foreman in the building trade (Case 5) trombone player (Case 15) and electrical engineer (Case 18) The other 4 patients are now performing light work.

Heart action is still controlled by the pacemaker in all 16 patients who are still alive In 11 patients the pacemaker has been used continuously for 6 months or more the longest follow-up time exceeds 2 years. (Case 1 was operated upon on Sept 19 1959)

Repeated estimations of threshold values for effective stimulation have been made on the patients with an external pacemaker the results are summarized in Table II As can be seen a stimulus strength of 4.5 volt has been sufficient in most cases. A temporary increase in threshold has been observed in 3 patients (altogether four times) On each occasion the increased threshold has been associated with an inflammatory process in the vicinity of the electrodes. Case 4 was found at operation to have an acute (nonbacterial) pericarditis

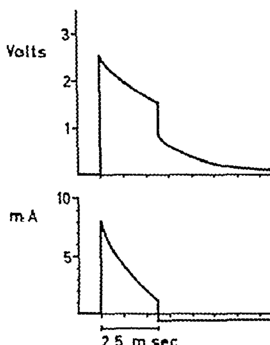


Fig 5 Schematic drawings of time-course of voltage and current for one pacemaker impulse. Each rapidly reaches peak value and then decreases along logarithmic curve After 2 5 msec. the voltage rapidly falls toward zero As result of the condenser coupling the current then is reversed and low current flow for considerable time in the opposite direction. The net flow of current during each impulse thus equals zero. All statements of impulse strength (expressed in terms of voltage or current) in the text concern "initial or peak" voltage and current



Fig 6 Roentgenogram of the chest showing myocardial electrodes applied to the anterior wall of the heart.

Table I Summary of cases

Case	Sex Age	Case history (time expressed in relation to date of operation)	ECG during attack (if recorded)	Main indication(s)* for operation
1	R.R. M 68	1 year earlier few AS. For 3 months AV II-III with several AS almost every day	Asystole	1
2	S.O. F 68	Sporadic AS for 2 years. Rhythm changing between AV I and III. Acute deterioration with very slow irregular rhythm and numerous AS	Asystole	1 + 2
3	H.R. M 75	Occasional AS for 2 years. Last 5 months permanent AV III with periods of pronounced bradycardia but no AS. Slight decompensation, aggravated when AV III supervened		3
4	A.E. M 39	Sudden AV III with ventricular rate of 15-20 per minute, acute decompensation and during a week some 20 AS	Asystole	2 + 3
5	T.C. M 57	AV block for 5 months, last 3 months permanent AV III with slow fixed rate. About 30 AS of severe character	Ventricular tachyarrhythmia	2 + 3
6	K.K. M 66	1-2 weeks 4 AS of severe character. Between attacks, mostly AV I but for 15 to 45 minutes after each attack AV III		2
7	S.S. M 60	Atrial fibrillation since age of 40. For 4 years, sporadic AS, increasing frequency last 6 months	Asystole	1
8	H.K. M 69	Sporadic AS for 5 years, periods of very frequent attacks (max. 150 short attacks a day). Between attacks, AV I (idioventricular beat never recorded)	Asystole	1 + 2
9	H.H. M 46	AS for 15 months, altogether 3 to 400 attacks. Rhythm changing between AV I, II and III. Moderately severe mitral stenosis	Asystole	1
10	L.L. M 55	For 8 months AS of varying frequency. Last 2 months permanent AV III and no AS	Asystole	3
11	V.S. M 63	During 1 month about 20 AS of severe character. Between attacks, AV I-II	Asystole	2
12.	A.P. M 56	For 2 years, AS of increasing frequency, altogether 40 attacks. Between attacks mostly AV I but after each attack period of AV III with slow rate (12 to 20 per minute)	Asystole	1

*1 Chronic form of Adams-Stokes syndrome. 2 Acute arrhythmia with high-grade A-V block and Adams-Stokes attacks. 3 Complete
†Chest: Precordial area. Groin: Region above left groin.
AS: Adams-Stokes attacks. AV I, II, III: Atrioventricular block of first, second, and third degree.
Table I is continued on pages 738-739.

Type of pacemaker and place of exit of percutaneous leads†	*Follow-up time beginning December 1961*	*Present status with regard to the heart*	*Comments*
External Chest	2 y 3 mo.	Good	
External Chest	1 y 8 mo.	Good	8 months after operation infection of thoracic wall successfully treated
External Chest	1 yr 3 mo	Good	
Implanted. After 4 wk. changed to external because of increased threshold	1 y	Good	Pericarditis, verified by biopsy 3 weeks after operation failure of stimulation, resumed after increase of amplitude. 10 months after operation infection of thoracic wall, successfully treated
External Chest. 7 mo. later changed to implanted	9 mo.	Good	
External Chest	8 mo	Good	
Implanted	8 mo.	Good	Transient hemiplegia of right side after operation
External Groin	8 mo.	Good	
External Groin	7 mo.	Good	Mitral commissurotomy performed at same operation. Ventricular fibrillation on fifth day after operation, presumably due to faulty pacemaker successfully treated
External Groin	6 mo	Good	Loss of close contact between electrodes and myocardium (demonstrable by use of stimuli slightly below threshold and radiographically)
External Groin	6 mo	Good	Perimyocarditis, verified by biopsy. Dislodgement of electrodes observed several months after operation. Resulting rise of threshold could be overcome by increase in stimulus amplitude
Implanted	5 mo	Good	

[illegible] block with slow and fixed ventricular rate.

Table I Summary of cases—Cont d

Case Sex age	Case history (time is expressed relation to date of operation)	ECG during attack (if recorded)	M in indication( )* for operation
13 A.L. M 21	Heart enlargement, paroxysmal atrial tachycardia grossly abnormal ECG. A week before operation AV III and numerous AS spontaneous reversion Recurrence of attacks, requiring immediate operation	Asystole	2
14 N N F 3	During 6 weeks altogether 10 AS of severe character Rhythm changing between AV I and III	Asystole	1
15 V K. M 57	During 3 years, changing rhythm and many AS Last 4 years permanent AV III with slow fixed rate, and no AS	Asystole	3
16 M L F 60	5 months earlier some 10 AS Since that time permanent AV III with slow fixed rate and no AS		3
17 H A. M 74	For 1 month AV III with slow fixed rate and pronounced restriction of activity Sudden deterioration with numerous AS of severe character	Ventricular tachyarrhythmia	2 + 3
18 H L. M 47	During 3 years, frequent AS but last 4 years permanent AV III with slow rate and often irregular rhythm accompanied by spells of dizziness	Asystole	3

the symptoms of which subsided during the following months In Case 11 a biopsy specimen showed a perimyocarditis. The second rise in threshold in Case 4 and the transient increase in threshold in Case 2 both occurred in connection with infection of the thoracic wall (to be described below)

On a few occasions the rise in threshold has caused failure of stimulation which has resulted in intermittent myocardial response or complete inefficiency of stimulation with reappearance of the spontaneous rhythm that existed before operation Rarely has such failure of stimulation been accompanied by syncopal attacks. By increasing the impulse strength it has always been possible to resume effective stimulation

Measurements of threshold are not possible on patients with an implanted pacemaker As in these cases failure of stimulation has not been observed and since the output voltage of this apparatus is 6.5 volts, it can be concluded that the threshold is below this value in each case.

The close contact between myocardium and electrode has been lost in the 3 patients who have inflammatory processes near the electrode and in one other patient (Case 10) who did not show any signs of inflammation Detachment of one or more electrodes in these cases has been demonstrated radiographically either by conventional radiograms or by cinefluorography The latter method allows recording of the movements of the electrodes and it is possible to determine whether they closely follow the movements of the heart. When they do not it is assumed that the electrodes have become adherent to the tissues outside the heart. As a result the efficiency of stimuli that slightly exceed threshold will vary with posture and with different phases of respiration. A further moderate increase in stimulus strength has been found in these cases to result in constant effective stimulation regardless of body position

Negative stimuli are more efficient for excitation[24] and when two myocardial electrodes are used the excitation will usually start at the negative one Therefore a change in polarity will result in a change in configuration of the pacemaker-induced ventricular complex (Fig 10)

The impedance between the electrodes

could be heard. The dose of hydrochlorothiazide was decreased to 25 mg. daily. By July 13, while he was on a hypocaloric diet alone, his weight was 191 pounds. On no occasion had there been significant deviation in the level of his therapeutic hypoprothrombinemia.

It should be emphasized that this patient was purposely not given digitalis initially. Moreover, this drug proved not to be necessary after his subsequent diuresis and decrease in body weight.

Case 8. Successful management of acute pulmonary edema in a cardiac patient of normal weight. F. M., a 65-year-old white woman, was seen for the first time in acute pulmonary edema of several hours duration. There had been no anginal pain, peripheral edema, or thrombophlebitis. She had experienced an acute coronary episode approximately 1½ years previously and heretofore was maintained uneventfully on digitoxin (0.1 mg. daily). The pertinent findings on physical examination included tachycardia, occasional ventricular premature beats, enlargement of the heart, and extensive crepitant rales bilaterally. The cardiomegaly and pulmonary congestion were confirmed by x-ray examination. Left bundle branch block, ventricular premature beats, and digitalis effect were noted in her electrocardiogram.

This patient was hospitalized, placed in oxygen, and started on benzthiazide (50 mg. twice daily). Initially she was given a single injection of a mercurial diuretic. Her diet consisted solely of formula (one glass four times daily) and water in limited amounts. On this program, her dyspnea rapidly decreased. There was a decline in weight from 132 pounds on admission to 125 pounds by the third hospital day. The levels of serum electrolytes and transaminase were normal. The dose of oral diuretic was decreased to 50 mg. daily. She was discharged 4 days after admission on a standard low-sodium diet, an increased dosage of digitalis and benzthiazide.

Case 10. Successful management of congestive failure in a nonobese patient after failure to respond to digitalis and diuretics, spironolactone elevated. M. Z., a 79-year-old man with longstanding arteriosclerotic heart disease, was seen on Jan. 3, 1962, because of progressive congestive failure manifested by intense shortness of breath, auricular fibrillation, hepatomegaly with epigastric tenderness, and an increasing bilateral pleural effusion. Previously he had been on maintenance Lanoxin, hydrochlorothiazide, supplementary potassium, and multivitamins. Fluids were being forced because of an infection of the renal tract. The patient had lost all desire for food because of his constant nausea and epigastric discomfort. Evidence of marked muscular wasting and early digitalis toxicity also was found. His weight was 149¼ pounds at the first visit. He did not wish to be hospitalized.

The initial therapeutic approach consisted of continuing the previous medication, reducing his intake of fluids, and insuring adequate nutrition at bedtime and during the night. The patient weighed 151 pounds when seen 2 days later. However, at that time, a pleural effusion that involved the lower one third of the right lung field was seen in his chest films.

The patient was then placed on six glasses of formula daily—including one glass during the night—with supplementary oatmeal and bananas. He also was shifted to benzthiazide (50 mg. daily) and was given an injection of a mercurial diuretic. One day later (January 6) his weight had decreased from 151 to 144¼ pounds accompanied by a marked reduction in the dyspnea. Thereafter, he was continued on a standard salt-poor diet with recommendations to use water sparingly and to continue his other medication. Several injections of parenteral vitamins also were given. A course of spironolactone was contemplated but his response to the above-mentioned program and to a second injection of a mercurial diuretic proved to be so gratifying that this was no longer regarded as necessary. By January 11, his weight had decreased to 138¾ pounds, the lung fields were clear, his liver was no longer palpable, and x-ray examination showed a striking regression of the pleural effusion. Seven weeks after initiating formula, he was free of edema and dyspnea on limited activity.

Case 11. Management of anasarca in a patient with arc nemoles and probable cardiac and pleural metastases treated with spironolactone. F. H., a 47-year-old white woman, was hospitalized on April 6, 1962, because of increasing edema of 2 months duration, as evidenced by extensive bilateral pleural effusions, ascites, and marked edema of the lower extremities. She was found to have had an adenocarcinoma of the uterus 8 years previously; radium and x-radiation therapy were then administered. Three years prior to hospitalization, metastases to the cervical and axillary lymph nodes were found and proved by biopsy. She had done quite well thereafter until several months prior to admission when she developed pneumonia, after which her congestive symptoms progressed. She had been drinking much fluid and was using salt without restriction. When she was first seen, the dyspnea and anasarca were striking. Her pulse was 116 and regular. The blood pressure was 170/70 mm. Hg. Enlarged nontender nodes were present in the neck and axillae. There was evidence of fluid in both lower lung fields. No obvious cardiomegaly or murmurs were detectable. In addition to moderate ascites, a prominent pelvic mass could be felt.

The presence of an extensive bilateral effusion was confirmed by x-ray examination. The patient's electrocardiograms revealed low voltage, sinus tachycardia, and nonspecific flattening of the T waves. No obvious metastatic lesions could be detected in her chest films nor in the x-ray films of the upper gastrointestinal tract, skull, pelvis, or other bony structures. The pertinent laboratory findings on April 7, 1962, were as follows: sodium 137.5 mEq./L., potassium 4.15 mEq./L., chlorides 96.3 mEq./L., total serum bilirubin, 1.5 mg. per cent, BSP 42.3 per cent retention at 45 minutes, total protein, 5.32 Gm. per cent, with albumin of 2.29 Gm. per cent and globulin of 3.03 Gm. per cent, serum transaminase 310 units.

The patient weighed 140 pounds when admitted to the hospital. She had a slight body frame and was approximately 5 feet 3 inches tall. She was started on one half glass of formula every 3 hours

Type of pacemaker and place of exit of percutaneous leads†	*Follow-up time beginning December 1961*	*Present status with regard to the heart*	*Comments*
External Groin	(8 days)	Death 8 days postop.	Ventricular fibrillation on eighth day after operation, probably unrelated to pacemaking Autopsy showed severe cardiomyopathy of unknown cause
Implanted	4 mo.	Good	
Implanted	3 mo.	Good	
(Implanted intended)		Death at operation	Death from repeated ruptures of very fragile myocardium Autopsy showed recent (approximately 12 hours) myocardial infarction
External Groin	2 mo.	Good	
Implanted	1 mo.	Good	

is of the same order in all cases (mostly 200 to 300 ohms) It does not change appreciably with time. A change in distance between the myocardial electrodes affects the impedance to a very small extent

Failure of stimulation due to the breaking of an electrode lead has not occurred

Complications

Artificial pacemaking can give rise to certain complications Two of these infection and pacemaker induced tachyarrhythmia are intimately related to the mode of treatment

Infection The placing of foreign material inside the body carries with it a risk of infection A slight redness and a serous secretion close to the place of exit of the electrode cables has often been observed for a few weeks after operation. In several patients who have had percutaneous leads for a long time short funnel-shaped skin pocket have developed around the leads and all sign of inflammation have disappeared

In 2 patient (Cases 2 and 4) bacterial infections of the thoracic wall occurred (after 8 and 10 months respectively) In each an abscess was formed around one of the electrode leads. After appropriate drainage, removal of the electrode involved and intense antibiotic treatment the infections subsided. These patients were primarily supplied with two myocardial electrodes and in each case the unaffected electrode could be spared By insertion of an indifferent electrode subcutaneously continued pacemaking has been possible.

At first the leads were taken out through the chest wall but in the later cases extension of the subcutaneous route of the leads to the region above the left groin has been preferred (Table I) In the 6 patients so treated no infection has as yet been met with.

One patient (Case 7) was primarily supplied with an external pacemaker Upon his urgent request this was later changed to an implantable one, which was connected to the same leads. Two weeks postoperatively a seropurulent secretion from the operation wound was noted but after antibiotic treatment the infection disappeared

Infection has not occurred in ar

tient with a primarily implanted pacemaker

Severe arrhythmias during pacemaker stimulation It is well known that ventricular fibrillation can be initiated by a single short electrical stimulus provided that it is strong enough It must also reach the myocardium during the vulnerable period e.g a certain phase of late systole which approximately coincides with the first part of the descending limb of the T wave

Brooks and associates[24] have shown that the electrical stimulus will produce single extrasystoles series of extrasystoles short periods of ventricular fibrillation and finally permanent fibrillation as the strength is successively increased The phenomenon of more than one extrasystole caused by one single stimulus is called *repetitive firing* and might be regarded as a premonitory sign of ventricular fibrillation

On one occasion only short periods of repetitive firing have been observed (Fig 10)

Ventricular fibrillation has been encountered twice and these episodes will be described briefly

Case 9 After implantation of myocardial electrodes pacemaker of another make was used at first. A small lamp on this pacemaker marked each impulse and on two or three occasions it was observed that the blinks were not quite regular An electrocardiographic tracing also shows irregular stimulation (Fig 11). On the fifth day after operation, irregular blinks were again noted, and, in addition the patient experienced a few short attacks of syncope. Arrangements were made to change the pacemaker but before this could be done the patient suddenly became pulseless.

Closed-chest cardiac massage was performed by the ward personnel for some minutes, after which an acute thoracotomy was undertaken. The heart was found to be fibrillating but after defibrillation with electrical countershock and connection of the leads to another pacemaker the rhythm was again stabilized. The patient recovered without signs of cerebral injury and is now in good condition.

The temporal relationship between a demonstrated technical fault of the pacemaker and the attack of ventricular fibrillation makes it probable that the arrhythmia was caused by overstimulation from the faulty pacemaker

Case 13. Eight days after operation this patient had three short Adams-Stokes attacks. Attention was directed to the possibility of arrhythmia caused by overstimulation and the stimulus amplitude was decreased therefore, to slightly above threshold value. A cardioscope for continuous monitoring of the electrocardiogram was connected. After a short while, ventricular fibrillation was noted. An acute thoracotomy was undertaken in order to defibrillate the heart, but, when the pericardium was opened, the arrhythmia reverted spontaneously and the heart action immediately became controlled by the pacemaker (see Fig 13). The electrocardiogram after reversion also showed some extrasystoles without the temporal relation to the pacemaker stimuli that is characteristic of repetitive firing. Some 15 minutes later ventricular fibrillation recurred. Several attempts to defibrillate were without effect and the patient could not be saved. Autopsy disclosed a grossly enlarged heart (825 grams) with no valvular or vascular lesions, but with hypertrophy and marked variation in size of the muscular fibers. The case may be classed tentatively among idiopathic cardiac hypertrophies.

The recurrence of fibrillation despite a considerable reduction in stimulus strength and the spontaneous reversal during continued stimulation make it improbable that the arrhythmia was caused by the pacemaker The severe pathologic changes in the myocardium might be responsible for the occurrence of ventricular fibrillation

Discussion

The encouraging results obtained in 16 of the 18 patients show that artificial pacemaking can be successfully accomplished by the technique described The majority of patients have been observed for more than 6 months and in all it has been possible to continue effective cardiac pacemaking In the absence of certain complications such as infection the threshold for myocardial excitation appears to remain at a fairly constant level Probably pacemaking may be effectively maintained for many years.

Stimulation rate For long term artificial pacing of the heart, we have used a fixed stimulation rate. In spite of this, all patients have been able to adapt themselves to a fair degree of physical activity and the patients who had complete heart block before operation no longer have experienced a troublesome limitation of physical activity When heart rate cannot be varied regulation of cardiac output and oxygen transport to the tissues must be achieved by variation of A V oxygen difference and stroke volume [25,26]

Table II Threshold for effective stimulation at different times after operation

Case	Time after operation	Threshold values		Initial impedance (ohms)	Comments
		Voltage (volts)	Current (ma.)		
1	11 mo.	2.8	0.5	300	
	20 mo.	2.2	6.5	340	
	27 mo.	2.0	7.0	290	
2.	4 mo.	3.3	11.0	300	
	9 mo.	6.5			Infection
	14 mo.	1.6	5	320	
	19 mo.	1.7	5.2	325	
3.	At operation	1.7	6.5	260	
	4 mo.	2.1	8.1	260	
	12 mo.	1.3	4.4	300	
	15 mo.	2.0	6.5	300	
4	1 mo.	4.2	18	230	Pericarditis
	3 mo	8			
	4 mo	6	25	240	
	7 mo	4.5	19.5	235	
	10 mo.	12.5	50	250	Infection
	12 mo	5.8	30	195	
5.	At operation	1.9	8	240	
	4 day	2.0	8.3	240	
	1 mo.	1.8	8.5	210	
	7 mo	2.0	8.0	250	
6.	2 mo.	3.2	13	250	
	9 mo	4.3	18	240	
8	2 mo	1.4	4.5	310	
9	2 mo.	2.2	11	200	
	8 mo	2.5	11	230	
10.	4 days	1.2	6	200	
	5 mo.	2.7	11	250	
11	1 mo.	2.7	12.5	215	Perimyocarditis
	3 mo.	5.8	29	200	Dislodgment
	6 mo.	7.0	36	195	of electrodes
17	10 day	1.9	7.0	270	
	1 mo.	2.3	8.0	290	
	2 mo.	3.0	12	250	
	4 mo.	2.8	11	255	
7 12 14 15 18	1-8 mo.	<6.5			Implanted pacemakers measurements not possible

A regulation of heart rate according to variable physiologic needs might be achieved by electronic transmission of the atrial impulses to the ventricles [11] or by manual adjustment of the pacemaker rate by the patient We have experience only with the latter method and we have found that most patients do not easily

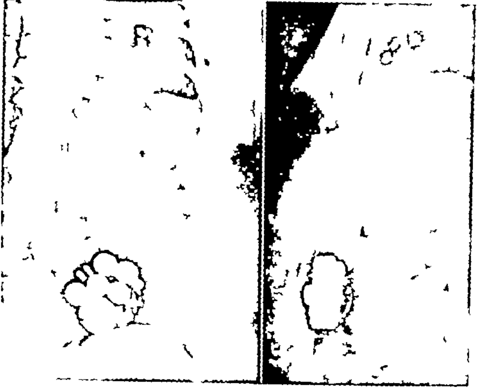


Fig. 7. Anteroposterior and lateral views of the upper part of the abdomen, showing pacemaker placed in the anterior abdominal wall. Two electrodes are connected to the pacemaker; the third one is a reserve, and the corresponding lead lies subcutaneously lateral to the other ones.

understand how to adjust the frequency in a suitable way.

The advantage of a simple and dependable stimulator unit, in our opinion, for the present outweighs the advantage of variability of stimulation rate, which must necessarily make the pacemaker more complicated.

The question of which fixed frequency is most suitable for long-term pacemaking cannot be easily answered today, and probably individual differentiation (according to duration of block, age of patient, etc.) would be indicated. In the frequency range of 40 to 100 per minute, higher rates often result in a better physical working capacity[11] and may also prevent or decrease signs of congestive heart failure.[11,27,28] On the other hand, high rates might lower the mechanical efficiency in aged or hypertrophied hearts and further impede coronary blood flow in patients with atherosclerotic heart disease.

A third factor of importance in some cases is the requirement of a certain minimum frequency for prevention of paroxysms of ventricular tachyarrhythmia.[22] Two of our patients (Cases 5 and 17) had such attacks, which disappeared after operation. Case 17 even had repeated attacks during operation, and these were completely abolished as soon as effective pacemaking was started.

Until more is known about how to decide on a suitable rate, we prefer for the present to use a frequency of 75 impulses per minute for the internal pacemaker. When an external pacemaker is used, the same frequency is usually employed.

In Cases 1, 3, and 11 the rate was lowered to 42-46 for 2 to 4 weeks after several months of continuous pacemaking with a rate of 75 per minute. In each case symptoms and signs of congestive heart failure appeared: dyspnea, peripheral edema, pleural effusion, and pulmonary congestion. All 3 patients improved rapidly when the rate of stimulation was again increased to 75 per minute.

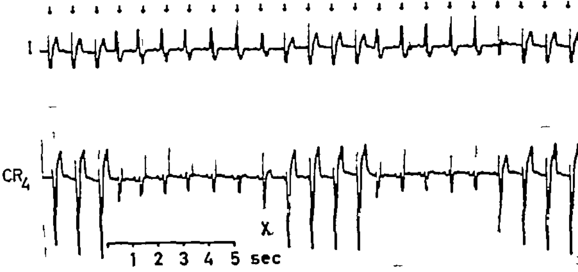


Fig. 8. Electrocardiogram showing interference between supra ventricular nd pacemaker-induced beats (Case 6). The spontaneous hythm is sinus rhythm with prolonged A V conduction time (0.25 second) and a left bundle branch block. During pacemaking an interference pattern (actually parasystolic rhythm) of spontaneous and pacemaker-induced beats is obtained. Atrial frequency is 60 and timulation frequency is 66 per minute. The stimuli are not effectiv when they occur during the refractory phase, which in this ase was found to extend pproximately 0.30 second from the beginning of the QRS. When timulus occurs just before the QRS, the ventricles are simultaneously activated by the normal route and from the pacemaker and "fusion beat is recorded *(marked by an X)* *(For larity each pacemaker impulse has been indicated by an arrow.)*

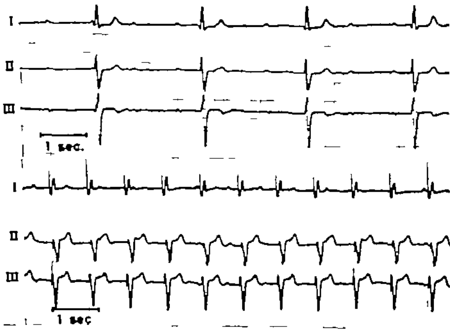


Fig. 9. Electrocardiogram from case of complete heart block before and after operation (Case 18). *Upper tracing* Idioventricular rhythm w th rate of 26 per minute. *Lower tracing* Pacemaker-induced ventricular beats with rate of 74 per minute. \ spontaneous entricular activity

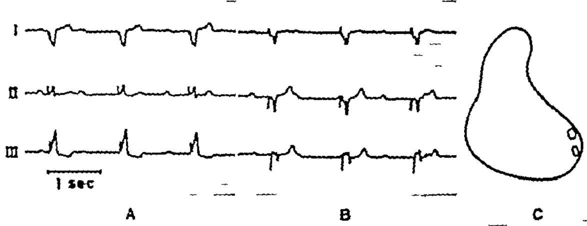


Fig. 10. Electrocardiograms showing the effect of reversion of polarity during stimulation between two myocardial electrodes (Case 3). A, Negative impulses to upper electrode. B, Negative impulses to lower electrode. C, Schematic drawing of the heart indicating position of the two electrodes in the frontal plane.

Fig. 11. Repetitive firing. This phenomenon should be regarded as a premonitory sign of ventricular fibrillation. The electrocardiogram was obtained in Case 17 after measurement of the stimulation threshold. The threshold was determined by a variable pacemaker with a frequency of 50 impulses per minute and amounted to 1.9 volts. Upon disconnection of this impulse generator, an idioventricular rhythm was immediately established. Another pacemaker was connected and, with an impulse amplitude of 3.8 volts and a stimulation frequency of 27 impulses per minute, short periods of ventricular tachyarrhythmia occurred. These were completely abolished by an increase in the rate of stimulation without a reduction in stimulus strength. (For clarity, each pacemaker impulse is indicated by an arrow.)

When a spontaneous supraventricular rhythm exists, an interference rhythm can be recorded during pacemaking (see Fig. 7). This rhythm will be slightly irregular and the mean frequency will depend both on atrial and pacemaker rate. In these cases the heart rate will increase during exercise because of acceleration of supraventricular impulse formation.

Electrodes. Today, the greatest problem in developing a reliable method for artificial control of heart activation concerns the myocardial electrodes. No general agreement exists on the most suitable type of electrode and this fact is reflected by the many constructions in use at present.

Among the prerequisites for maintenance of effective stimulation are constancy of threshold and reliable fixation of the myocardial electrodes. The stimulation threshold is determined by the myocardial excitability in a strictly physiologic sense and by the distance between electrode and myocardium. Most variations of threshold (Table II) are presumably due to differences in distance. The close range of threshold values obtained by measurements very soon after application of the elec

trodes (6.0 to 8.0 milliamperes)—when scar tissue has not yet formed—speaks in favor of this supposition

A layer of connective tissue of a certain thickness around the electrode will influence the excitatory effect of a large electrode proportionately less than that of a small electrode. The epicardial placement of the electrodes and the use of materials that do not give rise to strong inflammatory reaction were adopted with the aim of avoiding abundant formation of fibrous tissue. We are inclined to believe that the comparatively stable threshold values obtained are due to the construction of the myocardial electrodes.

A reliable fixation might be achieved by placing the electrodes intramurally in the ventricular wall and intramyocardial electrodes have been used by most workers.[3, 14] In our series, detachment of one or more electrodes has occurred in 4 patients, 3 of whom had however an inflammatory process near or in the heart wall At the moment we are testing certain modifications in the means of attachment of the electrodes. By creating a local adhesion between the two layers of the pericardium around the site of each electrode, and by carefully avoiding traction of the leads, we hope to obtain a better fixation

Myocardial excitability In the clinical application of electrical stimulation of the heart attention must also be paid to the variations of myocardial excitability in a strict sense. Principally the impulse strength selected should (a) exceed threshold for myocardial excitation in diastole during different physiologic (and even some pathologic) states, and (b) be well below values at which ventricular fibrillation might be elicited.

A. MINIMAL REQUIREMENTS The relative effects on myocardial excitability of changes in vagal and sympathetic tone, of administered hormonal and pharmacologic agents, and of changes in heart rate have been extensively studied by several physiologists. Comprehensive reports can be found in the works of Brooks and associates[24] and Hoffman and associates.[10] The variations of excitability caused by myocardial disease are less completely known but a few studies of the effects of ischemia exist.[11] The excitability of ischemic heart muscle is lowered but the effects of ischemia generally are not uniform and some cells with almost normal excitability may be expected to be reached by the impulse.

B RISK OF VENTRICULAR FIBRILLATION Diseased hearts might fibrillate spontaneously A causal relationship between stimulation and ventricular fibrillation might therefore be impossible to establish unless an electrocardiographic tracing of the beginning of the fibrillation is obtained The conditions necessary for ventricular fibrillation to be elicited are stimulation during the vulnerable period and sufficient stimulus strength

The first mentioned condition will be



Fig 12 Case 9 Irregular impulses from pacemaker (of another construction than those described; see text). An unduly high stimulus amplitude is suspected because of the effectiveness of the stimulation very early after the preceding beat (on top of the T wave). The patient later collapsed from ventricular fibrillation, but this was successfully treated.

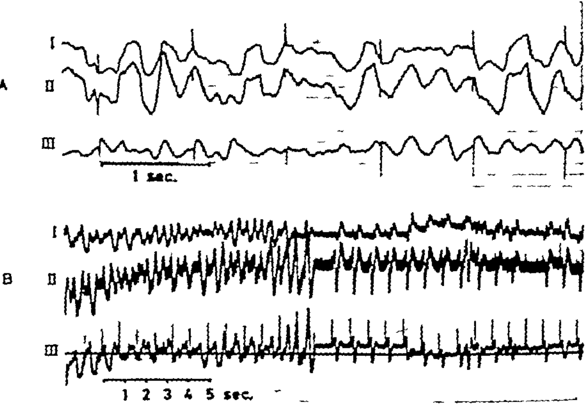


Fig. 11. Case 13. A, Ventricular fibrillation. B, Spontaneous reversion of arrhythmia and immediate return of pacemaker-controlled rhythm with some premature beats (one shown in record). The patient later succumbed because of recurrence of ventricular fibrillation (see text).

fulfilled if spontaneous beats interfere with the pacemaker-induced beats, such as occurs when A-V conduction is not completely blocked. In cases of complete heart block, a slow idioventricular rhythm is usually suppressed by stimulation with a faster rate. However, extrasystoles sometimes occur and an impulse may reach the myocardium during the vulnerable period of such a beat.

Of considerable importance is the ratio between the ventricular fibrillation threshold and the minimal effective pacemaker impulse (diastolic excitation threshold). This ratio has been found in animal experiments to amount to 10:1 or more.[4] The fibrillation threshold is considerably decreased by injection of sympathomimetic amines.

Wiggers and associates[33] first described the increased vulnerability to fibrillation during acute ischemia. MacLean and Phibbs[34] found the lowering of the fibrillation threshold after coronary ligation to amount to more than 60 per cent, and they also showed that this effect *remains* to a great extent when the examination is repeated 6 months after the ligation. Myocardial ischemia, reinforced by a period of slow idioventricular rhythm, might explain the occurrence of several short bouts of ventricular tachycardia observed in Case 17 (for description, see Fig. 11).

On the basis of these observations, theoretical reasoning leads to the conclusion that pacemaker-induced ventricular fibrillation *might occur* in certain cases with ordinary stimulation rate and with stimulus amplitude only moderately exceeding diastolic threshold.

Quite a different problem is the risk of accidental electrocution by defective pacemakers or by inadvertent connection of the myocardial electrodes to another source of current. A few such accidents have been reported.[23,24,25] Most risks may be abolished if battery-powered pacemakers are used, and if the circuit for recharging the capacitor (cf. Fig. 3) includes a high resistance.

The latter arrangement prevents the myocardium from being continuously exposed to the battery voltage if the second transistor should break down.

In our series, one episode of ventricular fibrillation seems to have been caused by irregular and probably too strong stimulation from a pacemaker The other case of ventricular fibrillation presumably had no causal relationship to pacemaking

Selection of stimulus intensity and type of pacemaker The results of the threshold determinations show that 4.5 volts will suffice in the great majority of cases. The implantable pacemaker gi ing 6.5 volts, is now used for most new patients.

The external pacemaker is preferred for patients with signs of acute myocardial disease. The voltage is adjusted according to the results of threshold determinations, and a margin of 50 to 100 per cent above threshold is usually employed. At present, patients with an active pericarditis are also supplied with an external pacemaker

Summary

1 During recent years the problems of artificial pacemaking of the heart have been approached in different ways. Tech nical construction of two types of pacemakers, developed by the authors and surgical procedure for application of the myocardial electrodes are described.

2 The main difference from the methods used by other workers lies in the use of rather large electrodes (9 mm in diameter) which are applied to the epicardial surface of the heart These electrodes were adopted w th the aim of obtain ng a stable threshold of stimulation

3 Clinical results in 18 patients treated by artificial pacemaker are presented Two patients died at or soon after oper ation In the other 16 patients the heart action is till controlled by a pacemaker The first patient in the series was operated upon in September 1959 and the follow up period exceeds 2 years and 3 months. Of the est 10 patients ha e been followed for more than 6 months.

4 Ventricular fibrillation has occurred twice one case t was due to a faulty pacem ker and in th other t was probably related to pacemaking

5 Se er l of th problems in olved in artificial pacemaking are discussed se lection of stimulation frequency choice of stimulus intensity and the risk of in duction of severe ventricular arrhythmias

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as her sole sourc of calories infrequent sips of w ter were taken desired She wa lso placed on digitalis nd g en three parenteral injections of a merc rial di retic er the ensuing week. She recei ed Aldactazide (1 tablet four times day) from April 8 t April 12 Th patient subsequent weights were as follow April 7—132 pound April 8 9 nd 10—131 pound April 11—130 pounds April 12—127 pounds April 13—125 pounds nd April 14—122 pounds. A thoracentesis of the left best was performed on April 11 and 1,000 ml of serou fl id w removed. On April 9 th patient serum sod um potassium and chloride le l were 137 5 3 55 nd 92 mEq /L respectively On April 13 these levels were 137 4 65 nd 94.5 mEq /L respecti ely Her total bilirubi had de cl ned t 0 8 mg per cent The total protein and lbumin had risen to 5 77 and 2 57 Gm. per cent, respectively Her serum t nsaminase had declined t 72 units

On April 14 the patient was concerned bout the formula repeating Accordingly she was started on 1.0-Gm. sodium diet with form la feedings between meal and t bedtime. Her weight was 120 pound by April 15 at which poi t the formula w discontinued I pat of the bove-mentioned profound diuresis, the patient, her relati es nd the ttending nurses commented bout her remarkable clinical improvement including the subsidence of dy pnea and cough nd her se se of well being

Case 15 M nagement of postphlebitic syndrome with lymphedema E. H. 54 year-old female post office clerk had suffered from long-standing post phlebitic syndrome after her pregnancies. Two oper tion for ricose veins had been performed. When he wa fi st seen in J nuary 1958 because of chronic bronchial sthma nd a respiratory infection her weight wa 147½ pound Sh was 5 feet 8 inches tall and of moderate body build Symptomatic osteoporosis also wa present, for which combined hormone therapy nd supplementary alc m were prescribed. She then gained weight progressively reaching 174 pounds on F b. 29 1960 Her presenting difficulty at that time was increasing pain, swelling nd tenderness of the lower legs, complicated by the development of leg ulcerations. Thi disorder was particularly important and distressing in view of the prolonged st nding entailed by her occupation.

The patient was continued on her previous medication. An ointment which contained neomycin nd dexamethasone wa pplied to the lesion several times daily I addition she was placed on formula (four glasses daily) her sole source of calories. By March 8 1960 he weighed 166¼ pounds nd wa feeling exceptionally well. At that poi t he alternated 3 day of formula with 4 days of a low-salt hypocaloric diet. She also took Metrec l wafers a needed for hunger By March 25 1960 h weight had declined to 158¼ pounds, the swelli of the lower limbs had decreased nd the super ficial ulcerations were completely healed. With the use of elastic stockings and regula period of rest off her feet this patient ha had no further signif icant difficulty with her legs during the ensuing 2 years of observation.

Case 16 M nagement of po tphlebitic syndrome in an obese patient W C a 65-yea -old male retail tore clerk had been experiencing attacks of pain, swelling nd discoloration of the left lower ex tremity for over 30 years. He had undergone prolonged studies nd hospitalizations for this disorder including 51 days in Veterans Administration Hospital for an ulcer of the left leg 1 year prior to his first visit A ligation of varicose veins had been performed 4 years previously When first seen after another such episode in June, 1959 his weight was 246 pounds. He was 6 feet 1 inch tall nd of large body build Gout was excluded It was thought that the patient was experiencing recurrent thrombophlebitis and a postphlebitic syndrome, both being further aggravated by his obesity

The patient was given counsel concerning bed rest avoidance of leg crossing, the use of bland soaks, and a topical steroid-containi g ointment. Several injections of corticotropin gel were administered. On a modification of his regular diet, his weight declined t 238 pounds. On June 19 1959 he wa placed on formula for 7 days, supplemented by one glass of grape j ice daily By June 29 hi weight wa 227¼ pounds. He volunteered the information that he felt unusually well and that hi leg ppeared to be better than it had been in years. At that point he was placed on standard 1,200 calorie diet without added salt. When he wa seen 3 weeks later however his weight had in creased to 230 pounds. Formula wa then resumed By A gust 7 his weight had declined to 220½ pounds. On a subseq ent modified dietary regimen that consisted of the formula and hypocaloric feed ings, hi weight decreased t 216¼ pounds by September 11 By this time the patient had resumed hi occupation with minimal difficulty On October 9 1959 his weight wa 211 pounds.

Comment

Many physicians experience considerable (and justified) misgivings as to whether their patients are actually receiving a diet which contains 1 0 Gm or less of sodium as prescribed—even in hospitals staffed by dietitians Heretofore this has constituted a major advantage of the standard or modified Karell diet since one could thereby control not only the amount of fluid being consumed but also the intake of sodium The present study was one directed primarily toward preventing hospitalization of outpatients nevertheless there are obvious practical implications for the management of edematous individuals who are hospitalized (viz. Cases 6 13 and 20) In Case 20 a diet of 1,200 calories and 800 mg of sodium was specifically prescribed after a gratifying 14½-pound diuresis had been achieved on formula for previous refractory heart fail ure. Total daily urines were collected and

A study of acute myocardial infarction at the Seraphimer Hospital during 1950-1959

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This paper is based on retrospective data from the hospital records of all patients with acute myocardial infarction who were treated in the medical department of the Seraphimer Hospital during the 10-year period 1950-1959. The object has been to present a clinical study and to compare the results with those of some similar studies.

The hospital is one of the university hospitals in Stockholm and receives the majority of its patients from a nondefined population in Stockholm and its environs. The patients in this material represent a certain selection from the population in general and the material is not suited for epidemiologic studies. However, the basic conclusive data correspond well with those of some other unselected Scandinavian materials which will be discussed in detail.

The case records, laboratory tests, electrocardiograms, and x-ray examinations were not made uniformly, so that the evaluation of some data was difficult or impossible. Only data which are considered to be representative of the total material are presented in this study.

Selection of cases

All clinical records registered with the diagnosis of myocardial infarction were reviewed. A sample of 200 records registered with the diagnosis of cardiosclerosis was also studied, but no cases of acute myocardial infarction were found. Twenty-three records were missing at the time of the study. The data from these are thought to be not relevant to the figures of the material.

The patients included in the study were admitted to the hospital in connection with the onset of their myocardial infarction and in addition also a small number of patients whose initial illness had occurred from 2 days up to 3 weeks before admission, but whose histories, electrocardiograms, and laboratory tests showed a still active myocardial process.

The diagnosis was based on a combination of the patient's history, clinical picture, electrocardiogram, and laboratory tests, such as erythrocyte sedimentation rate, white blood cell count, and fasting blood sugar. Since 1956 determination of the enzymes GOT (glutamic oxaloacetic acid transaminase), GPT (glutamic pyruvic acid transaminase), and LD (lactic acid dehydrogenase) have been used routinely.

All autopsy records from the medical department during the period 1950-1959 were studied. Of all the patients who died in the medical department, 85 per cent were autopsied as compared to 87 per cent of the patients with myocardial infarction. In 16 per cent of the patients who at autopsy were found to have died from myocardial infarction this diagnosis

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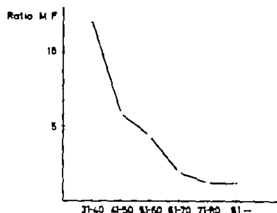


Fig. 1. Variation of the ratio of males to females by age

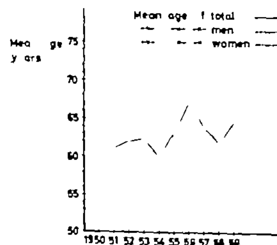


Fig. 2. Mean age per year during 1950-1959

had not been made clinically. In 5 per cent of the patients with a clinical diagnosis of myocardial infarction the diagnosis was not verified at autopsy.

The material included also the patients who died within a few hours after they had been admitted to the hospital. These patients did not influence significantly the figures on the accuracy of the clinical diagnosis.

Patient material, age and sex ratio

The material consisted of 667 patients. Five hundred forty-six patients had had one myocardial infarction, 94 had had two, and 27 had had three or more.

There were 471 men and 196 women, which gives a sex ratio of 2.4. For the patients with one, two, and three myocardial infarctions taken separately the corresponding figures were 2.1, 4.2, and 8.0, respectively.

The ratio of men to women was highest in the younger age groups and approaches 1 with increasing age, which is shown in Fig. 1. The same is found in all other comparable materials. The reason why young men are more prone to myocardial infarction than young women is not fully understood.

The mean age of the total material was 63.1 years, 61.4 years for the men and 67.2 years for the women. The mean age showed quite large annual variations (see Fig. 2). There seems to be a tendency toward increasing mean age. During 1950-1954 the mean age of the total material was 61.7 years and during 1955-1959 it was 64.2 years; the increase was significant ($p < 0.001$).

The mean ages of the patients with one, two, or three myocardial infarctions are shown in Table I. In the total material there were no significant differences between these mean ages. The low mean age of the patients with three or more infarctions, especially during the later 5-year period when the group consisted of 15 men and no women, is remarkable but may be the result of coincidence and the small number of patients. The mean age of these patients at the time of their first infarction was 56.3 years.

The distribution of the patients among the age groups and the sex ratio is shown in Fig. 3. The largest age group was 61-70 years, comprising 36 per cent of the total material. Eighty-three per cent of all the patients fell into the age group 51-70 years.

Preceding diseases

The patients in this material presented a variety of preceding diseases, but special mention will be made only of hypertension, diabetes mellitus, and angina pectoris.

Hypertension. Only patients who had been treated and controlled for high blood pressure prior to their infarction and/or who were found to be hypertensive during their hospitalization were included. No untreated patients with a vague history of occasional high blood pressure were included. In this study the criteria for hypertension were a diastolic blood pres-

Table I Mean age of the patients with one two and three myocardial infarctions during 1950 1959

Period	Mean age (years) of patients with		
	1 infarct	2 infarcts	3 infarcts
1950–1959	63 2	63 4	62 0
1950–1954	61 7	60 0	67 5
1955–1959	64 3	65 6	57 7

sure of more than 95 mm. Hg on repeated recordings in patients under 60 years of age, or more than 100 mm Hg in patients over 60 years of age

One hundred thirty-one patients, 50 men and 81 women constituting 19 6 per cent of the total material were included This figure differs markedly from the 42 per cent of the Malmö material [3] in which study the criterion for hypertension was a blood pressure of more than 150/100 mm Hg and from the 44 per cent of the Uppsala material in which study the criteria for hypertension were a blood pressure of more than 170-160/100 mm. Hg in patients over 60 years of age and 150/95 mm Hg in patients under 60 years of age According to Plotz, one finds figures of 25 to 75 per cent in the literature One of the reasons for these discrepancies probably is the difference in the criteria used

The mean age of the patients with hypertension was 66.2 years 63 4 years for the men and 67 9 years for the women. This mean age was 3 8 years higher than the mean age of the patients without hypertension the difference was significant ($p < 0.001$) † The difference was not due to a few very old patients with hypertension but mainly to a large number of patients who were 71 to 80 years of age (see Fig 4) Also in the Malmö material[3] the mean age of the patients with antecedent hypertension was higher than the mean age of those without hypertension.

This observation is somewhat surprising inasmuch as one would perhaps expect a lower mean age of the patients with antecedent hypertension since hypertension is known to affect the cardiovascular system in a deleterious way [19] However one cannot exclude the possibility that factors of selection may have played a role in this material

The ratio of men to women in the group of patients with hypertension was 0 6 as compared to 3 7 in the group of patients without hypertension the difference was significant ($p < 0.001$) This inversion of the sex ratio is generally found also in other materials. Possible explanations are a slightly higher prevalence of hypertension among women than among men in the higher age groups of the general population and the fact that women outnumber men in the same age groups of the general population It is interesting that the sex ratio for hypertension in the general popu

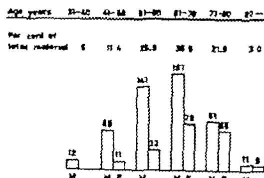


Fig 3 Age and sex distribution of the total material.

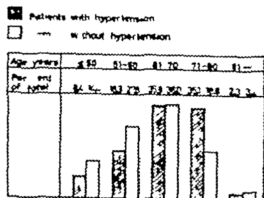


Fig. 4 Age distribution of the patients who had myocardial infarction for the first time with and without hypertension.

*In the infarction material from 1940–1941, which consisted of 202 patients, the corresponding figure was 36 per cent (unpublished data).

†In the infarction material from 1940–1941 the corresponding mean age was 64 8 years, which was identical with that of the rest of the material (unpublished data).

lation of the Bergen study[11] is exactly the same as in this study using the same criteria for hypertension From these figures it does not seem that men are more vulnerable to hypertensive heart disease than are women

Diabetes mellitus Fifty nine patients 8.8 per cent of the total material had diabetes mellitus. There were 37 men and 22 women which gives a sex ratio of 1 7 The mean age was 63 5 years 60.2 years for the men and 69 0 years for the women None of these figures were of significant difference from corresponding figures for the rest of the material

The prevalence of diabetes mellitus in materials of myocardial infarction varies very much According to Plotz,[9] one finds from 7 9 to 17 5 per cent in the literature. The Malmö material[3] had 9.8 per cent the Uppsala material had 8 2 per cent, and some other Swedish materials had 4 0 6 1 and 17 8 per cent.[4 7 11]

In this material there were more diabetic men than women the opposite was generally found in other materials.[13 14] Also the mean age of the diabetic patient was not different from that of the rest of the material whereas other authors [13] have found a slightly higher mean age of the diabetic patients in myocardial infarction materials.

Angina pectoris prior to myocardial infarction This group consisted of patients who had only one myocardial infarction and a history of antecedent angina pectoris. Two hundred thirty-nine patients, 43 7 per cent of those who had myocardial infarctions for the first time, belong to this group. The corresponding figure in the Uppsala material was 60 per cent[4] and in the Malmö material 50 per cent.[15]

There were 151 men and 88 women, a sex ratio of 1 7 which is of no significant difference from the 2.5 for the patients without antecedent angina pectoris. The mean age was 64 4 years 63 2 years for the men and 65.3 years for the women which figures are not significantly different from those of the rest of the material

Patients without antecedent diabetes mellitus hypertension or angina pectoris One hundred forty nine patients 27.3 per cent of those who had myocardial infarction for the first time were included. There were 123 men and 26 women a sex ratio of 4 7 which is of significant difference ($p < 0.001$) from the figure 1 7 for the rest of the patients with one myocardial infarction The mean age was 59 2 years which is of significant difference ($p < 0.001$) from 64 6 years for the rest of the patients with one myocardial infarction The mean age of the men was 57 9 years and that of the women was 65.3 years.

This group of patients differs markedly from the rest of the patients with only one myocardial infarction It is interesting that in the 6-year follow up of the Framingham study[16] the ratio of men to women in the group of patients with one myocardial infarction without antecedent coronary heart disease was 4 0 as compared to 4 7 in this material. It is remarkable that in this group of patients, in whom the myocardial infarction is the first sign of coronary heart disease the mean age is significantly lower than that of the rest of the material and especially lower than that of the patients with hypertension and diabetes mellitus, which diseases are said to be risk factors in the development of coronary heart disease.

Laboratory tests

Electrocardiograms Electrocardiograms were recorded in 635 patients, 95.2 per cent of the total material Routinely the three standard leads, $CR_{1\,2\,4\,5\text{-}7}$ Wilson 1 2-4-5-7 aV_R, aV_L, and aV_F leads were used all in all 16 leads. In 87 0 per cent of the patients the electrocardiograms were thought to be consistent with acute myocardial infarction and in the rest no evidence for this diagnosis was found All the recordings which were considered to be pathologic were not of the classic type with pathologic Q wave S-T segment elevation and negative T wave. Some recordings were thought to be positive if they showed only ST T and T wave changes indicating an active myocardial process, and the patient's history and laboratory tests confirmed the diagnosis.

The 87 per cent of pathologic electrocardiograms in this study is considerably higher than the 64 per cent reported in Grewin's study [15] in which however only electrocardiograms of the "classic" type were considered to be positive. With the use of a twelve-lead system Anastasiadis

Table II. Frequency of peripheral thromboses, embolisms, hemorrhages, and cardiac ruptures in the anticoagulant-treated patients

	Number of patients	Per cent of total
Total	569	
Peripheral thromboses	5	0.9
Peripheral embolisms	11	1.9
Hemorrhages	10	1.7
Cardiac ruptures	10	1.7

Table III. Mortality of patients with one, two, and three or more myocardial infarctions

Number of infarcts	Number of patients	Number of patients who died	Mortality (%)
1	546	171	31.3
2	97	35	37.2
3 or more	27	15	55.6
Total material	667	221	33.1

Table IV. Mean age of patients who survived and of those who died, and mortality of men and women

	Mean age			Mortality (%)
	Total	Surviving	Dead	
Total material	63.1	61.7	66.0	33.1
Men	61.4	60.1	64.1	32.4
Women	67.2	65.6	70.3	34.6

and Sivertson found diagnostic electrocardiograms in 88 per cent of the cases, and according to Plotz,[9] one gets diagnostic electrocardiograms in at least 95 per cent of the cases when using 12 leads.

Enzymes. GOT, GPT, and LD were determined in 219 patients. The values were considered to be diagnostic of myocardial infarction in 207 (95.5 per cent) of the patients. In some of the negative tests the samples of blood were taken too late after the acute infarction to be of diagnostic value.

White blood cell count. This was considered to be pathologic if there was an elevation of the count to at least 9,000 cells per cubic millimeter. The count was made in 557 patients, 83 per cent of the total material, and was pathologic in 66 per cent of the patients.

Erythrocyte sedimentation rate. This was considered to be pathologic if more than 20 mm. The test was made in 580 patients, 87 per cent of the total material, and was pathologic in 81 per cent of the patients.

Rectal temperature. This was considered to be pathologically elevated if over 37.0° C. in the morning and 37.8°C. in the afternoon for 2 consecutive days. Temperature was recorded in 615 patients, 92.2 per cent of the total material. Pathologic elevation was found in 86 per cent of the patients.

Treatment

Anticoagulant treatment was used routinely during the whole period if there were no contraindications. There was no untreated control group.

Five hundred sixty-nine patients, 85.3 per cent of the total material, received anticoagulants. Four hundred sixty-six patients received both heparin and dicoumarol, and 103 received only dicoumarol. Heparin, 400 to 500 mg., in three to four doses intravenously was given during the first 2 days. Dicoumarol was given orally from the beginning.

The frequency of peripheral venous thromboses and embolisms, hemorrhages, and cardiac ruptures is shown in Table II. It should be mentioned that of the 10 patients with hemorrhagic complications, 2 had intracerebral hemorrhages, with fatal outcome (one of the patients had hypertension), 1 had severe nasal bleeding, and 1 had a bleeding duodenal ulcer. The other 6 patients had intracutaneous hematomas or hematuria that were without further clinical significance.

Mortality

In the total material of 667 patients, 221 died, which gives a total mortality of 33.1 per cent. One hundred fifty-three men and 68 women died—a sex ratio of 2.3. The mortality figures for the patients with one, two, or three infarctions were 31.3, 37.2

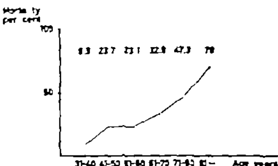


Fig 5 Mortality rat per age group.

and 55 6 per cent respectively which are shown in Table III There is no significant difference between these figures. This is in accordance with observations from Malmö

The mortality of the first 5 year period w s 29 1 per cent and of the second period 36 1 per cent. The difference is probably due to a higher mean age of the total material during the second period but the difference is not significant.

The mean age of those who survived and of those who died and the acute mortality of the men and women are shown in Table IV The mean age of those who died was higher than that of those who survived both in the total material and in men and women separately both differences were significant ($p < 0.001$)

The acute mortality rose with advancing age as is shown in Fig 5 which finding is confirmed in almost all materials. Because the women have a greater mean age than that of the men one would expect a higher mortality for them. This was not the case in this material the women had approximately the same mortality as the men i.e., 34 6 and 32 4 per cent, respectively In several other materials the women carry a higher mortality [1,9] which is attributed to their greater mean age.

Twenty-eight per cent of the total mortality occurred during the first 24 hours of hospitalization and 63 per cent during the first 10 days.

The total mortality is reduced to 26.2 per cent when the patients who died during the first day of hospitalization are excluded.

The acute mortality of the patients with hypertension was 29 7 per cent that of the patients with diabetes mellitus was 40 6 per cent and that of the patients with antecedent angina pectoris was 28 0 per cent. The patients who had no hypertension diabetes mellitus or angina pectoris prior to the myocardial infarction had a 24 8 per cent mortality None of these figures differ from each other significantly

The clinical causes of death are shown in Fig 6 Shock and pulmonary edema are by far the leading causes and together are responsible for 55.2 per cent of the total mortality

The mortality figures of this material seem to be quite ordinary In some other comparable Scandinavian materials one finds a mortality of from 23 4 to 55 per cent [1, 4-6,11,3, 41] and in some British and American materials the figures are 27 6 to 53 per cent according to Plotz.[9] This wide divergence cannot be assigned solely to differences in treatment, but must also be ascribed to differences in the general

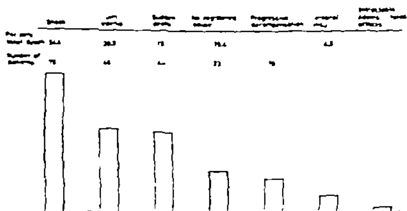


Fig 6 Clinical causes of death

population and its hospitalization facilities, different mean ages of the materials different criteria of diagnosis, different incidence of severe cases and many other factors. It seems that the mortality rate in Scandinavian materials from the last 10 years is about 30 per cent.

In this material preceding hypertension diabetes mellitus or angina pectoris had no significant prognostic influence on the acute mortality In other materials at least diabetes mellitus was found to carry a bad prognosis for the acute mortality [illegible] whereas angina pectoris and hypertension seemed to have no influence. [illegible]

Shock In this study the criteria for shock have been a typical clinical picture of peripheral coldness moist skin tachycardia, disturbed sensorium etc combined with a fall in blood pressure below 100 mm Hg systolic for at least 30 minutes

According to this definition shock occurred in 88 patients, 13 1 per cent of the total material. There were 63 men and 25 women, which gives a sex ratio of 2.5 as compared to 2 4 for the rest of the material The mean age of the patients in whom shock occurred was 64.3 years, which is not significantly different from the 63 0 years for the rest of the material

The mortality rate of the patients in whom shock occurred was 84.3 per cent as compared to 24.8 per cent for the rest of the material the difference is significant ($p < 0.001$) The mean age of the patients who survived was 60.1 years, and that of those who died was 64 9 years the difference was not significant. Ten patients were younger than 50 years of age and carried a mortality of 80 per cent, as compared to 87 per cent in the patients who were more than 50 years of age

The percentage of patients in whom shock occurred was approximately the same in all age groups.

Forty five patients were treated with intravenous infusion of norepinephrine in either 5 per cent glucose solution blood or macrodex the mortality in these patients was 82 7 per cent. According to the records the shock was not considered to be severe in 3 of the surviving patients.

In 23 patients who were treated with oxedrine or other sympathicomimetic drugs intramuscularly the mortality rate was 78.2 per cent.

Patients in shock were always treated as soon as possible. The duration of shock before the beginning of treatment could not be estimated with exactness from all records.

The records of the other 20 patients contain no information on the eventual specific antishock treatment. The records do not indicate whether treatment was deliberately withheld or whether the patients died before treatment could be given. The mortality rate in these patients was 100 per cent.

In comparison with other materials, the incidence of shock in this material (13 1 per cent) is low and the mortality rate is high (84.3 per cent) This divergence is probably due to different criteria for shock. With the criteria used in this study the cases may be considered to be severe. In two other materials[illegible] with comparable diagnostic criteria and treatment the mortality was 100 per cent According to some other authors, [illegible] one finds mortality rates ranging from 33 to 88 per cent. In some Swedish materials the severity grouping of Helander[1] has been used according to which the Group I patients are those who during the first 24 hours after the clinical onset of the myocardial infarction show symptoms of shock or hypotension to values below 100 mm Hg in systolic pressure (in patients with previous hypertension a fall to less than two thirds of the previous systolic pressure) In these materials [illegible] the mortality of the patients in this group has ranged from 57 to 79.8 per cent.

Pulmonary edema Pulmonary edema occurred in 73 patients, 11 per cent of the total material. There were 46 men and 27 women, a sex ratio of 1 7 which is not significantly different from the 2.4 in the rest of the material. The mean age was 66.6 years, as compared to 62.7 years for the rest of the material and the difference is significant ($p < 0.001$) The routine treatment consisted of intravenous digitalis, oxygen theophyllamine morphine derivatives and the use of the cardiac bed or sitting position The mortality was 63 per cent, which is of significant difference ($p < 0.001$) from the 29 4 per cent for

the rest of the material. There was no difference in age between those patients who survived and those who died. In 17 patients with both shock and pulmonary edema the mortality was 100 per cent.

Summary

The material consists of 667 patients with acute myocardial infarction who were treated at the Seraphimer Hospital during the period 1950-1959. There were 471 men and 196 women, which gives a sex ratio of 2.4.

The mean age of the total material was 63.1 years: 61.4 years for the men and 67.2 years for the women. The mean age seemed to be increasing over the period of time covered.

Hypertension was present in 19.6 per cent of the total material. The mean age of these patients was 66.2 years and the ratio of men to women was 0.6, both of which figures are of significant difference from the rest of the material.

Diabetes mellitus was present in 8.8 per cent of the material. The mean age and the sex ratio of these patients did not differ significantly from those of the rest of the material.

Antecedent angina pectoris was present in 43.7 per cent of the patients with one myocardial infarction. The mean age and the sex ratio of these patients did not differ significantly from the rest of the material.

Twenty-seven per cent of the patients with one myocardial infarction had had neither antecedent angina pectoris, diabetes mellitus nor hypertension. The mean age of these patients was 59.2 years and the sex ratio was 4.7, which figures differ significantly from those of the rest of the material.

Electrocardiograms were diagnostic of myocardial infarction in 87.0 per cent of the patients. The enzymes GOT, GPT, and LD showed diagnostic elevations in 95 per cent of the patients. Pathologic elevation of white blood cell count, erythrocyte sedimentation rate, and temperature occurred in 66, 81, and 86 per cent of the patients, respectively.

Routine treatment during the whole period consisted of heparin intravenously and dicoumarol orally.

The mortality rate of the total material was 33.1 per cent. The mortality of the men and women did not differ significantly. The mortality rate rose with advancing age, and the mean age of those patients who died was significantly higher than that of those who survived. Hypertension, angina pectoris, and diabetes mellitus had no significant prognostic influence on the acute mortality.

Shock occurred in 13.1 per cent of the patients, with a mortality of 84.3 per cent. The mean age and sex ratio of these patients were not significantly different from those of the rest of the material.

Pulmonary edema occurred in 11 per cent of the patients, with a mortality of 63 per cent. The mean age of these patients was significantly higher than that of the rest of the material, but the sex ratio showed no significant difference. The combination of shock and pulmonary edema carried a mortality of 100 per cent.

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Coronary arteriovenous fistula with patent ductus arteriosus

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Coronary arteriovenous (A-V) fistula is a rare entity, but the hemodynamic strain which this lesion imposes on the heart makes its diagnosis important. The lesion can be suspected clinically. Surgical correction is, as a rule, relatively simple and has already been accomplished in 26 reported cases.[1-3]

Association of patent ductus arteriosus with coronary A-V fistula has been documented in 4 cases. Both lesions were surgically corrected in 2 of these cases although the diagnosis of coronary A-V fistula was not made preoperatively.

The patient whose case is reported in the present communication is the first in whom both a coronary A-V fistula and a patent ductus arteriosus were diagnosed preoperatively and corrected in a single operation.

Case report

A 6-year-old girl was referred to the Pediatric Cardiac Clinic for evaluation of a murmur discovered during a pre-school physical examination. There were no symptoms referable to the heart. There had been one episode of bronchopneumonia in infancy. Subsequently, upper respiratory infections were frequent.

The blood pressure at the time of her admission to the hospital was 100/60 mm.Hg and the pulse rate was 84. The peripheral pulses appeared to have a bounding quality. Additional pertinent findings were limited to the heart.

The cardiac pulsations were not remarkable to palpation. There was a thrill throughout the cardiac cycle, maximal at the fourth *right* intercostal space. A continuous, superficial Grade 4 (out of 6) "machinery" murmur was maximal at this location and was widely transmitted over the precordium and back. The intensity of the murmur was approximately the same in systole and diastole. The second heart sound at the pulmonary area appeared to be normal in intensity and in the degree of splitting. Roentgen and fluoroscopic examination revealed increased pulmonary vascular markings, exaggerated hilar pulsations, moderate generalized cardiomegaly and a definitely enlarged left atrium (Fig. 1). The ECG was within normal limits (Fig. 2,A).

The clinical diagnosis was coronary A-V fistula communicating with the right side of the heart, probably the right atrium.

Catheterization of the right side of the heart was performed as previously described (Table I). All pressures in the lesser circulation were at the upper limits of normal. The diagnostic series of blood samples revealed a left-to-right shunt at the level of the upper right atrium and mouth of the superior vena cava. The entrance of a shunt into the lesser circuit in this location was confirmed by indicator dilution techniques. The shunt was calculated to be of such magnitude that pulmonary flow was not quite twice systemic. There was no evidence of secondary rise in oxygen content at the pulmonary arterial level. These results were interpreted as being consistent with a coronary A-V fistula draining into the right atrium.

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analyzed on the last day of the formula diet and when on the 800-mg sodium diet there being no other change in therapy The levels of sodium and chloride while on the prescribed diet exceeded by 14 and 4 mEq./L. respectively the concentrations while on the formula.

Although this report deals with the management of edema in patients who have heart failure and the postphlebitic syndrome I also have observed significant regression of edema in patients with other edematous states on a regimen comparable to that described herein For example a 47 year-old man (J L.) with an alcoholic type of cirrhosis complicated by intense jaundice severe hypoproteinemia hypoprothrombinemia and slight hyperammoniemia was hospitalized because of massive anasarca Diuretics were purposely withheld for fear of precipitating acute hepatorenal failure. Within 11 days of formula (one-half glass every 3 hours) there was remarkable clinical improvement accompanied by a diuresis of 30 pounds (205 to 175 pounds)! Regression of edema also has been observed in patients who have become edematous while receiving adrenocortical steroid therapy

The effectiveness of the thiazide diuretics and spironolactone in the management of edema and effusions due to cancer[n] may be enhanced by such a practical method for both restricting fluid and sodium and insuring adequate intake of protein—as shown by Case 13 The restriction of fluid is particularly pertinent when inappropriate secretion of antidiuretic hormone complicates malignancy

The importance of dietetic management in congestive heart failure and other edematous states has been underscored by recent further insights into the role of aldosterone therein—and the inherent limitations of aldosterone inhibitors. Whereas the oversecretion of aldosterone appears to represent an important mechanism in the pathogenesis of edema associated with nephrosis and cirrhosis, the rate of secretion of aldosterone in advanced congestive heart failure has been found to be either normal or only moderately elevated even when such patients were receiving a low-sodium diet.[n] Paradoxically a rise in the rate of secretion of aldosterone can follow the addition of dietary salt, perhaps representing the aftermath of further renal retention of sodium with the added cardiac embarrassment so induced.[n] Other considerations that introduce reservations in the management of the edematous cardiac patient with aldosterone inhibitors at the expense of dietary management include the following (1) edema can persist—or even occur—in patients being treated with these drugs (2) edema can occur in the presence of potassium depletion with a lowered output of aldosterone and (3) certain normal individuals appear to be able to conserve sodium without increasing their output of aldosterone or when aldosterone is blocked by spironolactone.[n]

In patients who have congestive heart failure the patterns of electrolyte excretion associated with the diuresis induced by means of a prepared liquid low-sodium formula and bed rest—but without the use of diuretics—help in an understanding of the present observations. In one such study 15 edematous male patients received 2 liters of a formula derived from low-sodium milk, Casec dextrose cream and water this supplied approximately 1,950 calories 329 Gm of carbohydrate 63 Gm. of protein and 42 Gm. of fat daily[n] It was found that there were two patterns of the loss of edema i.e. loss of sodium of about 100 mEq per kilogram of weight lost, and loss of sodium of less than 50 mEq per kilogram of weight lost. These findings support the tenet that the loss of edema stems from both the excretion of excess sodium by the kidneys and a significant internal redistribution of sodium with osmotic inactivation of a portion of the ions in the edema fluid

The standard Karell diet consists of 200-ml. feedings of milk given at 4-hour intervals from 8 A.M. to 8 P.M. In this form it furnishes approximate amounts of the following protein 26 Gm carbohydrate 40 Gm. fat, 32 Gm. sodium chloride, 1 6 Gm. water 800 ml and total calories 552. The sodium content can be further reduced by the use of a sodium-poor milk (e.g Lonalac) Neither of these diets can be maintained without modification for more than several days, however because of their low protein content. It is my firm impression that patients on a sc

Aortography was then carried out by means of catheter introduced into femoral artery and ad anced toward the root of the aorta. At the level of the aortic knob, instead of passing to the right and dow into the ascending aorta, the catheter turned sharply to the left and downward into the pulmonary artery and right ventricle via a patent ductus arteriosus. The catheter was then redirected and passed into the ascending aorta.

The aortogram (Fig 3) revealed very much d'lated, somewhat tortuous essel which had the origin and course of a right coronary artery and which seemed to drain directly into the right trium *Immediate entrance of dye into the pulmonary artery as might be expected in the presence of* patent ductu arteriosus, was not noted. This study confirmed the clinical diagnosis and in addition demonstrated a patent ductus arteriosus which was otherwise obscured by the manifestations of the coronary A V fistula

Surgical correction was undertaken on Oct. 11 1960 through midline, longitudinal ternum plitting incision. The lesion was immediately apparent when the pericardium was opened. The left coronary artery ppeared to be normal, whereas the right coronary artery was dilated to diameter of pproximately 1 0 cm. and a vigorous thrill was palpated over it. From its normal origin the right coronary artery passed beneath the right trial *ppendage in the A V groove.* It then turned posteriorly instead of continuing in its usual course along the right lateral border of the heart, and entered the posteromedial wall of the right trium opposite the root of the aorta A single small branch arose from the mai trunk of the right coronary artery and passed downward along the anterior surface of the heart below the pulmonary artery

A ligature was placed around the main essel t its origin and another t its point of entry into the right trium. Temporary occlusion of either ligature eliminated the thrill and was w thout pparent effect on the color or contractility of the heart. The previously described branch was divided from the main trunk. The tw ligatures were then tied and the main essel was transected. At this time thrill was palpated over the intrapericardial portion of the left pulmonary artery Although the midline pproach does not afford liberal exposure of a ductus, *the latter was isolated w thout entry into the left* pleural space. The ductus, *of moderate caliber* was doubly ligated, after which procedure the thrill dippeared. The pericardium was then closed and the ternal margins were approximated with wire sutures.

The limb leads of the electrocardiogram were monitored during the operation. When the pericardium was opened, the T w ve became inverted in Lead I nd more so in Lead V_L. As each of the tw ligatures about the fistulous tract was tightened in turn these leads became normal, and again became bnormal when either ligature was loosened. When the ligatures were finally tied and the fistula was transected these abnormalities persisted.

The postoperative course was entirely uneventful. The *electrocardiographic abnormalities (Fig 2,B and C)* persisted for bout 5 days. Systemic hypertension to levels as high as 1 0/110 mm.Hg was noted during this same period. At the time the patient was discharged 10 days after operation physical examination of the cardiovascular system

Table I Data on catheterization of the right side of the heart

Catheter locatio	Blood oxygen ontent (Vols. %)	Blood pressures (mm.Hg)	
		Systolic/Diastolic	Mean
Innominate ei	9 3		
Inferior ena ca	9 4		
Superior vena ca	11 7		
Right trium			
High	11 5		
Mid	11 2 11 8		7
Low	11 2, 11 3		
Right entricle			
Low	11 3	30/8	
High	11 1		
Pulmonary artery			
Main	11 1		
Righ	11 5	30/12	18
Lef	11 2		
Pulmonary artery edge			10
Pulmonary ein	13 7		

Assumed

Total pulmonary flow about 44 per cent left-to-right shunt flow, or almost half of the lef ventricular output recirculates through the lungs The relative contribution to total shunt flow of each communication cannot be determined from the



Fig. 1 The posteroanterior chest film shows some increase in pulmonary vascular markings and mod- ... cardiomegaly. A double auricular contour was ... ed on the upper right heart border suggesting ... atrial enlargement.

...rmal except for Grade 1 systolic ejection murmur in the pulmonary area. This murmur subsequently disappeared. The child has shown spontaneous increase in physical activity and increased weight gain in the 20 months after surgery

Discussion

Congenital coronary A V fistula is usually an isolated clinical entity but it may occur by coincidence with another lesion as in the present case. It may also be a *component* part of a more complex malformation charactenzed by aortic or pulmonary valve atresia.

Initially recognized only at autopsy this lesion in its clinically important form was first successfully corrected when found unexpectedly in the course of surgery for anticipated patent ductus arteriosus.[11] Subsequently cases were suspected clinically and the diagnosis was confirmed by laboratory methods. The total number of cases reported to date is approximately 80 Many of the clinical features, as well as the relative frequency of communication of each coronary artery with the various drainage sites, have been amply covered in recent reviews.[1,3,7,11]

Apart from consideration as to which coronary artery is involved coronary A V fistulas have been classified either according to the chamber or vessel into which they drain[11] or according to whether the fistula enters a given chamber directly or via a vein[1] The designation coronary arterio-systemic has been applied to the rare instances in which the fistula drains into the left atrium or left ventricle. However the terms coronary A V fistula or "coronary artery fistula" appear to be acceptable when used in a generic sense regardless of the site or mode of drainage of the fistulous communication.

Coronary A V fistula is believed to result from the communication of a coronary artery or major branch (sometimes branches of each coronary artery) with large intratrabecular spaces (sinusoids) within the myocardium, which have failed to undergo normal condensation during fetal life. These communications constitute a low-resistance outlet through which coronary arterial blood drains directly into a heart chamber the coronary sinus a cardiac vein or the main pulmonary artery Marked often aneurysmal dilatation of the involved coronary artery usually results from the excessive flow of blood

Coronary A V fistula gives rise to the type of murmur associated with a rapid runoff of blood from the aorta at or near its root, and must be distinguished from other acyanotic entities which produce similar murmurs. These include patent ductus arteriosus, aortic septal defect, ventricular septal defect with aortic valve insufficiency aortic sinus fistula other intrathoracic arteriovenous fistulas, pulmonary artery stenosis, and anomalous coronary artery of the adult type.[14]

The murmur of coronary A V fistula may be indistinguishable from that of patent ductus arteriosus both in character and location. Clinical observations which may aid in the differential diagnosis of coronary A V fistula are these (1) The murmur usually seems "superficial" to auscultation. (2) Its location may be atypical i. e. below the usual site of ductus murmurs, or it may be maximal over the right side of the chest, as in the present case. (3) The diastolic component of the murmur may be louder than the systolic when the fistula drains into the right ventricle. (4) The association of a murmur and peripheral signs suggestive

of a large patent ductus arteriosus in the absence of radiologic evidence of a left-to-right shunt suggests coronary arterio-systemic fistula. (5) The dilated coronary artery may be seen as an excrescence on either border of the heart in the postero-anterior chest film.[13,17]

The data obtained by catheterization of the right side of the heart in this entity although often offering useful clues, are not pathognomonic. Aortography with injection of dye at or near the root of the aorta is the laboratory method of choice for demonstrating a coronary A V fistula since the fistulous tract is visualized unobscured by contrast material within the heart.

The physiologic importance of any coronary A V fistula depends on three factors (1) *The volume of shunt passing through it.* This, in turn depends on the smallest cross-sectional area of the fistula. As is true of any A V fistula the presence or absence of symptoms, cardiomegaly electrocardiographic evidence of ventricular strain or peripheral signs, such as bounding pulses, will depend on the proportion of left ventricular output which runs off through the low-resistance outlet offered by the fistula. (2) *The site of drainage of the fistula.* If the fistula drains into the left heart or the pulmonary artery the left ventricle alone is involved in the increased work load imposed by the lesion. In the latter instance, the hemodynamics are identical to those of uncomplicated patent *ductus arteriosus. If drainage is into the* right ventricle the work load of each ventricle is increased but the right ventricle is probably less affected than is the left

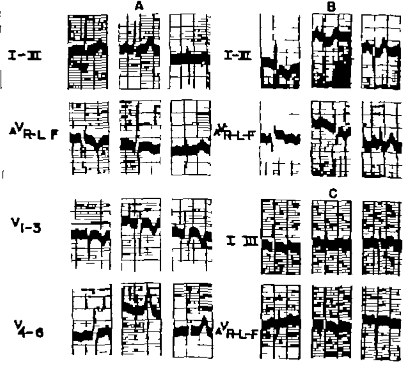


Fig 2 The pertinent electrocardiographic findings. *A* Prior to operation. The tracing is within normal limits. *B* Several hours after operation. Limb leads only The T wa is inverted in Leads I and V S-T is depressed and sagging in Lead II and sagging in Leads III and V The T w is taller i Lead III The abnormalities are nonspecific but could be due to myocardial ischemia. *C*, The day after operation. Limb leads only The S-T segments no longer deviate the T wave is less deeply inverted i Lead I and is diphasic, the terminal segment being upright, in Leads I and V_L. The T is smaller in Leads II III and V The abnormalities are now suggestive of left heart strain. Note V and V are reversed in the lower right-hand panel.



Fig 3 An early film in the aortographic series. The dye has advanced only as far as the upper portion of the descending aorta. A dilated and tortuous channel is seen passing to the right from the root of the aorta. This channel appears to drain jet fashion into the right atrium through two small terminal openings.

as in certain instances of ventricular septal defect If drainage is into the right atrium directly or via the coronary sinus, diastolic overloading of the right ventricle is proportional to the size of the shunt as in atrial septal defect although in a broader sense the hemodynamics here are analogous to those of A V fistula elsewhere in the body in that the same work load is imposed on both ventricles. (3) *The possible effects of the fistula or its surgical correction on the myocardial circulation itself* These effects will depend in part on individual anatomy An entire coronary artery may terminate in a fistulous tract or a major branch alone of either coronary artery may be involved. Arterial branches normal in appearance and seemingly normal in their connections, may or may not arise from the involved vessel.

If a coronary artery has a low resistance outlet it is to be expected that forward flow through any normally connected branches may be diminished Since this is a chronic state it is probable that collateral channels from the uninvolved vessel have compensated to the extent that myocardial flow from the abnormal vessel is compromised. As the amount of shunt flow through the involved vessel approaches its total flow the myocardial circulation approaches that of single coronary artery[1] i. e. the involved vessel is the afferent vessel of the fistula, whereas the uninvolved vessel supplies the myocardium The uninvolved coronary artery is usually of normal appearance as is the case in instances of *anatomic single coronary* artery (origin of entire coronary circulation from a single coronary ostium *)

The possibility that *myocardial ischemia* or reduced myocardial blood flow may be a direct consequence of coronary A V fistula has been *repeatedly stressed*,[1,3,13,24,25] but with little supporting evidence. Possible myocardial ischemia in association with coronary A V fistula has been reported only in the elderly There is little clinical electrocardiographic or pathologic[24,25] indication that any part of the myocardium is deprived of its supply of blood on account of such a fistula. Symptoms and heart size appear to correlate to the same extent with shunt size in coronary A V fistula as they do in other communications which allow a left to-right shunt.

Ligation of the involved coronary artery even at its ostium as in the present case, is well tolerated and there may be no associated electrocardiographic changes.[7,11,21,2] Any resulting electrocardiographic changes which might be suggestive of ischemia have usually been nonspecific and transitory [11,17,26] Thus in cases such as the present one the myo-

*In anomalous origin of the left coronary artery from the pulmonary artery[19] the myocardial circulation is also essentially that of anatomic single coronary artery The hemodynamic pattern, however, differs from that of coronary A-V fistula because both the myocardial flow and the precapillary runoff through the anomalously connected coronary artery (shunt flow) compete for the flow from the single normally attached artery rather than the shunt having an afferent limb of its own. The normally attached vessel is characteristically dilated and tortuous in this condition.

cardial circulation does not seem to depend to any extent on the involved coronary artery.

On the other hand, observations made during surgery suggest that in some cases the involved coronary artery or its branches do communicate functionally with the normal vascular bed of the myocardium. Electrocardiographic alterations which were interpreted as those of acute ischemia occurred in one instance when the fistula was occluded by interruption of the arterial supply near its origin; such alterations did not occur if the fistula was first occluded distally. This suggests that proximal occlusion converted the hemodynamics acutely into those of anomalous connection of the uninvolved coronary artery to the right side, so that precapillary deviation of some flow from this artery via the fistula then was responsible for the ischemic changes. In 2 cases,[illegible] electrocardiographic patterns of localized injury and ischemia showing the usual time evolution occurred after surgical correction of the fistula. In one of these cases[12] the electrocardiographic changes were associated with manipulation of a normally attached coronary artery branch which arose at the afferent end of the fistula. In the present case interruption of a small normally attached branch was without apparent effect.

Nonspecific postoperative electrocardiographic alterations could indicate surgical pericarditis or the nonspecific effects of surgery, as well as ischemia. Alterations during the days after operation in the present case were suggestive of left heart strain and occurred in association with transient systemic hypertension. We have observed a similar train of events after operation for patent ductus arteriosus, another instance in which acute interruption of abnormal runoff from the aorta can cause a sudden transient increase in resistance to left ventricular output. In the latter case the question of induced myocardial ischemia does not arise.

All of the foregoing considerations appear to indicate that interruption of a coronary A-V fistula is, in the main, innocuous. This would certainly tend to increase coronary flow through the normally attached branches of the involved coronary artery even though over-all effective coronary flow is probably uncompromised to begin with. When a fistulous main coronary artery is ligated at its origin, the myocardial circulation is definitively converted to that of single coronary artery.

The advisability of surgical correction of a coronary A-V fistula cannot be established solely on the basis of the natural history of the lesion, for such a lesion may give rise to symptoms in childhood[illegible] or, on the other hand, may be an incidental finding at autopsy in older persons. Symptoms have first appeared in later life,[illegible] and a fistula which does not interfere with normal existence for many years may still be the cause of death.[illegible] Favoring elective surgery is the fact that surgical treatment is, on the whole, technically easy and carries a low risk. Moreover, correction failed to result in clinical improvement in only 1 of the 25 surviving patients previously reported on, and in this patient the nature of the underlying pathology was not fully known.[14]

There has been only one operative death reported and this did not appear to be related either to the coronary A-V fistula itself or to its surgical correction.[4] Other factors also favor elective surgery. These are the actual or hypothetical complications of coronary A-V fistula, including congestive heart failure, pulmonary hypertension, subacute bacterial endarteritis, thrombosis or sclerosis of the fistula, or possibly coronary insufficiency in later years.

In the present case, cardiomegaly at an early age, the possibility that respiratory infections were related to the increased pulmonary flow, and the expected ease of surgical intervention were the factors regarded as sufficient grounds for elective surgery.

Coronary A-V fistula as an associated lesion has been discovered and corrected during surgery for patent ductus in 2 instances. In the first, a coronary A-V fistula was found at surgery to be the second lesion, of uncertain nature, suspected on the basis of the catheterization data. In the second, the patent ductus was the dominant lesion, and the coronary A-V fistula was unsuspected prior to oper-

ation In another case the two lesions were diagnosed with reasonable certainty on the basis of laboratory findings but surgical correction was postponed.[7] In the fourth case an inconsequential patent ductus arteriosus was found at autopsy of an infant with a large coronary A-V fistula. The present case is the fifth reported of such an association

Patent ductus arteriosus is a very common congenital lesion and there is little reason for regarding its occurrence with coronary A-V fistula as anything more than fortuitous. The present case however illustrates the difficulty in diagnosis that may be encountered when the two lesions coexist The murmurs produced are similar in quality and either lesion may give rise to peripheral signs. It is likely that the more dominant of the two lesions will obscure the signs which are more specifically suggestive of the other The dominant lesion in this case was the coronary A-V fistula. However the ductus was also significant in size despite the absence of a secondary rise in oxygen content of pulmonary arterial blood during catheterization of the right side of the heart and the absence of immediate entry of dye into the pulmonary artery during aortography These findings suggest that the dominant and more proximal runoff from the aorta (coronary A-V fistula) may have diminished the effect of the patent ductus arteriosus below that expected for its size Correcting only the coronary A-V fistula would have been analogous to using a peripheral vasoconstrictor agent to raise resistance to the normal aortic outflow in the presence of a patent ductus.[2] Thus had the ductus been missed it might well have become more significant hemodynamically as well as more obvious after operation.

The surgical approach to coronary A-V fistula may not be the ideal one for a patent ductus, as was true in this case This particular experience suggests that it might be wise to explore or at least palpate the ductus area in all cases of coronary A-V fistula coming to surgery

Summary

The first case is reported of coexisting coronary arteriovenous fistula and patent ductus arteriosus in which both lesions were preoperatively diagnosed and successfully corrected during a single operation. An attempt is made to outline the consequences of and practical approach to coronary A-V fistula based on the experience of the present case and a review of the pertinent literature. The problems inherent in the recognition of a patent ductus arteriosus in the presence of a hemodynamically dominant coronary A-V fistula are discussed.

Addendum

Since this report was submitted for publication 14 additional instances of successful surgical correction of coronary A-V fistula have been noted.[1-4] In two of these[1,3] the coronary fistulas were diagnosed after ligation of rather small patent ductus. In two cases,[1,3] the fistula itself was manifest in the posteroanterior chest film

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Origin of both great vessels from the right ventricle with pulmonary stenosis

Angiocardiographic findings

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We stated in a previous paper[1] that there is a *group of congenital defects* of the heart associated with stenosis of the outflow tract of the right ventricle and interventricular septal defect that should be called Fallot type complex.

The old concept of the tetralogy of Fallot as a nosological entity must be abandoned. We have shown that the *Fallot type complex* covers the *following groups*: (1) classic tetralogy of Fallot; (2) extreme tetralogy of Fallot (with pulmonary atresia or pseudotruncus arteriosus); (3) the so-called acyanotic or slight tetralogy of Fallot; (4) stenosis of the outflow tract of the right ventricle with interventricular septal defect and no overriding of the aorta; (5) partial *transposition* of both great vessels (or transposition of the ventricular chambers) with stenosis of the outflow tract of the right ventricle and ventricular septal defect; (6) single ventricle with pulmonary stenosis.

Another variety of malformation should be added. This consists of the origin of both great vessels from the right ventricle with stenosis of the outflow tract. It is extremely rare. The few cases described were diagnosed only at postmortem examination.[1-4]

Braun and associates described 1 case in 1952. Witham[7] (5 years later) mentioned 2 cases and designated them as double outlet right ventricle Fallot type. Recently Neufeld and co-workers[8] presented clinical, hemodynamic, and pathologic findings in 5 cases. They point out that *this condition is indistinguishable* from the tetralogy of Fallot on the basis of the clinical, electrocardiographic, and radiologic findings. The most recent case was a diagnostic error demonstrated at postmortem examination.

Therefore, to the six groups of our classification of the Fallot type complex, *a seventh group must be added*, which consists of double outlet right ventricle with stenosis of the outflow tract.

Diagnosis during life has been achieved for the first time in the case *now to be* reported.

Case report

The patient, L.F.M.C., was a 5-year-old girl. The mother states that until the third year of life the child became cyanotic and fainted only when crying. From then on, cyanosis became permanent

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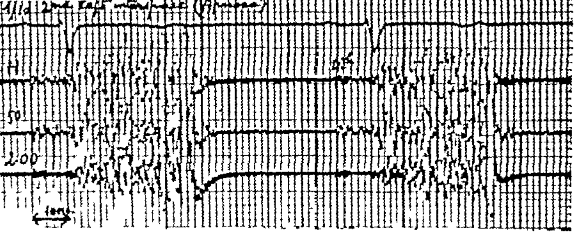


Fig 1 Phonocardiogram Second left intercostal space S stolic ejection murmur S 4 1/10 = Amplitude. H 50,200 = Frequency The depressed isoelectric line in the 200 f equency nge is due to amplitude of the second sound being too high to be managed by the mplifier



Fig 2 X-ray film of chest posteroanterior iew light bulging of the pulmonary contour

She as never subject to squatting Ther as history of f equent espir tory infections.

Physical exam nation The blood pressur was 90 65 mm Hg C anosis and clubbing of the finger as presen nd there as double-wa jugular pulse A light stolic thrill as audible in the suprasternal notch. There as lef thoracic deforma tion absenc of thoracic thrill loudness of the second pulmonary sound and ystolic ejection murm of Grade 3 of 4 intensit that as heard long he lef sternal border (see phonocardiogram Fig 1 The -r film of the chest (Fig 2) did not show he fe ures of the classic tetralogy of F llot but evealed instead slight bulging of the pulmonary ontour The electrocardiogram howed righ axis devia ion high peaked P w es in Leads II V V V V V V V high amplitude R av f om Lead V through Lead V and deep slurred S in Leads V and V changes consistent th right ventricular h pertroph (Fig. 3). I the ectorcardiogram he QRS loop was inscribed lockwise in the f ontal and horizontal planes as orientated inferiorly and took figure

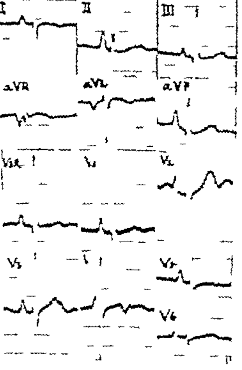


Fig 3 Electrocardiogr m. Right trial nd ventricular hypertrophy



Fig. 4. Vectorcardiogram. Right ventricular hypertrophy.

of-eight shape in the frontal plane. It was directed anteriorly and to the right in the horizontal plane consistent with right ventricular hypertrophy (Fig. 4).

Findings obtained by cardiac catheterization are shown in Table I. The catheter was inserted through the left saphenous vein. It entered the right atrium and then the left atrium and was also introduced into the right ventricle. The pulmonary artery could not be entered.

Two selective angiocardiographic series were performed with injection each time of 20 c.c. of a 76 per cent solution of Urographin at a rate of 4 exposures per second.

Table I. Catheterization data

Location of catheter	*Volumes % oxygen*	*Saturation (%)*	*Pressure (mm. Hg)*
Left atrium	18.3	92.5	10/4
Right ventricle	17.6	57.5	80/0

Fig. 5. Third exposure. *Left*, Posteroanterior view. *Right*, Lateral view. The right atrium is identified by the reflux of blood into the venae cavae and suprahepatic veins. The right ventricle is opacified. The arrows point out the tricuspid valve, which is open allowing the passage of the contrast medium (first angiocardiographic series).

milk program tend to become much weaker after their diuresis than do those given sodium-poor formula diets under similar circumstances. Moreover, the potential for incurring hepatic hypoglycemia when edematous patients are not fed after 8 P.M.—as alluded to previously—is a serious shortcoming of the standard Karell diet.

An advantage that a sodium-poor formula such as that employed has over the rice diet is the fact that the patient obtains from three to five times more protein, even though he ingests less than one half as many calories. For example, the Kempner diet (consisting of rice, fruit, fruit juices, sugar, and a vitamin supplement) furnishes approximately 2,000 calories, 15 to 30 Gm. of protein, 4 to 6 Gm. of fat, and 100 to 150 mg. of sodium daily. Nonobese individuals in calorie balance, however, are unable to maintain nitrogen balance on this amount of milk protein alone. Jolliffe has summarized the matter as follows: "Thus, with established methods of determining minimum protein requirements, one finds that 14 or 21 Gm. of milk protein and 30 to 40 Gm. of mixed proteins in a calorie-deficient diet given obese subjects could not be expected to maintain nitrogen balance prior to the time that the protein tissue mass had been reduced to such an extent that the decreased nitrogen consumption would allow maintenance of nitrogen balance. By this time the protein tissue mass would be so little and metabolism so low that the life of the patient would be in jeopardy."[11]

On repeated occasions the decrease in pre-existing hypertension after the loss of weight that stems solely from the use of formula diets has been impressive, often enabling the patient to decrease or discontinue potent antihypertensive drugs.[7] The reduction in blood pressure under similar circumstances has been shown to be more a function of the decrease in the intake of sodium chloride than of the loss of weight—the obese hypertensive patient perhaps being more sensitive than the nonobese to the restriction of salt.[12]

With the diversity of flavors and the introduction of the pudding and wafer forms of low-sodium formula diets, monotony and tastelessness can be obviated when a prolonged low-sodium diet is indicated—e.g., in obese patients who have accelerated (malignant) hypertension or refractory anasarca. Moreover, certain fresh vegetables that are relatively low in sodium content may be used as supplements, since it has been shown that the favorable effect of a low-sodium diet upon severe hypertension is not lost by the daily addition thereto of up to 50 Gm. of low-sodium protein and 200 Gm. of vegetables.[13] These could include cabbage, asparagus, okra, egg plant, mushrooms, lettuce, tomatoes, cucumbers, green peppers, radishes, and string beans. When the number of calories is not an important factor, lima beans, onions, squash, peas, corn, white or sweet potatoes, macaroni, spaghetti, rice, and fresh or water-packed fruits also can be recommended.

The high buffering capacity against gastric acidity of the formula used poses an added advantage in the management of cardiac patients.[6] There are many causes for gastrointestinal symptoms associated with congestive failure. These include the sequelae of acute and chronic enlargement of the liver, passive congestion of the abdominal viscera, compression of the esophagus by a dilated left atrium, atrophy of the pancreatic acini, therapy with various medications (viz., ammonium chloride, quinidine, the xanthines, chlorothiazide and its derivatives—particularly those containing added potassium[14]—reserpine, anticoagulants), azotemia, and sodium depletion resulting from excessive restriction of sodium and concomitant vigorous diuresis. There also appears to be a higher incidence of gastric ulcer in patients with failure due to arteriosclerotic heart disease.[7] The vulnerability of the small intestine in the course of congestive failure—as well as in myocardial infarction, subacute bacterial endocarditis, and occlusive thromboembolism of the abdominal aorta—further justifies the use of a nutrient with high buffering ability, especially in patients who have calcific aortic stenosis or in those who are receiving various pressor agents in large quantities.[15]

Other advantages of a formula that is relatively high in protein and low in carbohydrate include the minimizing of reactive hypoglycemia and the acute edema associated with glucose loading. With reference

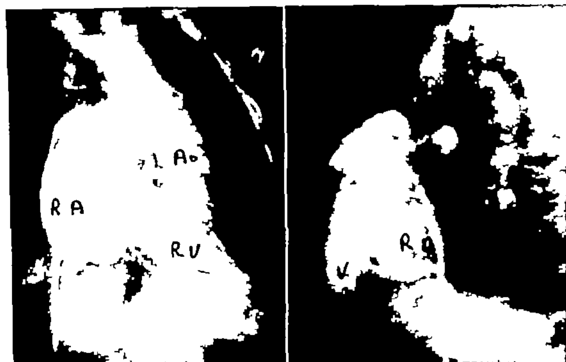


Fig 6 Sixth exposure *Left*. Posteroa terior view Aorta arises from the right ventricle in systole, forming the left contour of the cardiac silhouette. *Right:* Transverse iew show good visualization of the pulmonary artery the initial portion of hich is masked by the right trum (first angiocardiographic series).

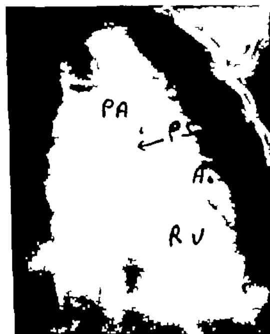




Fig 7 Thirteen h exposure posteroa terior plane. Stenosis of the pulmonary rtery (arrow) ith

Fig 8 Second angiocardiographic series. Second exposure LAO iew Contrast medium injected

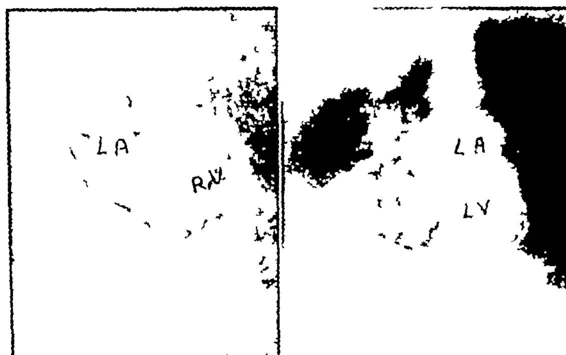


Fig 9 Th d exposur *Left* Right terior oblique iew *Right* Left nterior oblique view Beginning of passage of h m med m f om the left entricle into the right entricle The right anterior oblique iew shows the ferior on u of the aortic semil na cusps (second ngiocardiographic series).

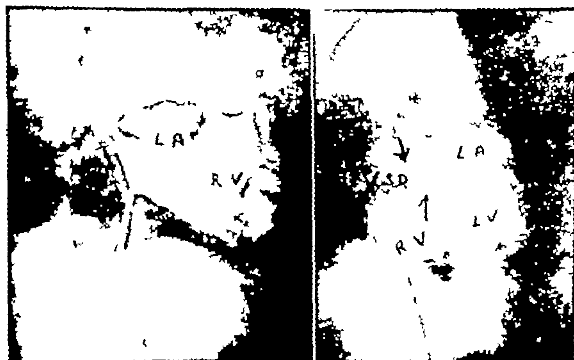


Fig 10 Fourth exposure *Left* Right erior oblique iew *R ght* Left anterior oblique iew More complet filling of the right entricle The size of the septal defect is marked in the left terior oblique iew by the arrows. I the right anterior oblique iew the inferior ontour of the aortic semilunar cusps is better depicted tha in the previou exposure (second ngiocardiographic series)



Fig. 11. Fifth exposure. *Left.* Right anterior oblique iew. *Right.* Lef terior oblique iew. The aorta and the pulmonary artery with its branches are simultaneously opacified in the t planes. The right terior oblique iew show ery clearly that the tw essels arise from the right entricle; the root of the aorta is placed laterally and teriorl and the pulmonary artery is situated posteriorly (dorsally) (second angiocardiographic series).

First giocardiographic series (2 planes simultaneously posteroan terior nd lateral). The catheter was located in the right entricle as show by he first angiocardiogram bu t the beginning of the i jection the catheter recoiled and remained in the righ uric la ppendage the injection as made i that cavity nd besides the uricular ppendage the right trium and the right entricle ere visualized. The third exposur learly shows the right trium identified by he refl of the dy the enae ca ae nd suprahepatic eins, ith the contrast medium passing into the right ventricle (the tricuspid al e is open), hich occupies its usual position (Fig. 5). The sixth exposure shows the aorta arising from the right entricle in ystole. The aorta occupies an entirely abnormal position rising on the left and forming part of he left contou of the cardiac shadow. The pulmonary artery and ts branches are seen below the right rium. The pulmonary rtery however is better depic ed the lateral plane hich show hat it ho rises f om he right entricle although its first portion is masked by the righ trium (Fig. 6).

The hirteen h exposure show by transparence cross of the pulmonary artery with poststenotic di tation (Fig. 7).

Second angiocardiographic series (2 planes simultaneously: right nterior oblique nd left anterior oblique). I jection was made in the left trium. The second exposure shows the left trium ith reflux of the contrast medium into the pulmonary veins, and opacification of the left entricle (Fig. 8). The third exposur show the beginning of passage of the contrast medium from the left the right entricle through septal defect (Fig. 9). I the fourth exposure there is almost complet filling of the right ventricle and the size of the interventricular septal defect may be evaluated (Fig. 10). I the fifth exposure the two planes show the sim ltaneous opacification of both the aorta and the pulmonary artery th its two branches, and the right anterior oblique plane shows that both the aorta nd the pulmonary artery arise from the right entricle the aortic sinf nd bulum occupying mor lateral position (Fig. 11).

The injection int he left trium, despit its great pressure did not provoke passage of the contrast medium i to the right trium. Therefore here is no trial septal defect but patent foramen ov le is present.

The comparison between the successiv angiocardiograms of both series (the first in the postero-

anterior and lateral positions and the second in the right anterior oblique and left anterior oblique planes respectively) shows that (1) The visualization of the two great vessels is simultaneous, and both arise from the right ventricle (2) The pulmonary artery begins to be visualized only after almost complete filling of the right ventricle (3) The only outlet to the left ventricle is the interventricular septal defect. (4) There is a pulmonary valvular stenosis with poststenotic dilatation. (5) The pulmonary circulation is poor (6) There is a wide interventricular septal defect

Discussion

The clinical features would suggest the diagnosis of an atypical Fallot complex. The clue to the correct diagnosis of the right ventricular origin of both great vessels can be obtained at the time of selective angiocardiography of the left side of the heart

After visualization of the left ventricle the right ventricle became opacified before visualization of the pulmonary artery the two vessels visualized simultaneously This finding is decisive for the elimination of the only valid hypothesis to be considered in the differential diagnosis namely the existence of a Taussig Bing syndrome consisting of complete transposition of the aorta and incomplete transposition of the pulmonary artery In this condition the pulmonary artery overrides the septum and its root is in relation with both ventricles In the Taussig Bing syndrome immediately after the filling of the left ventricle the contrast medium should enter simultaneously into the overriding pulmonary artery notwithstanding the valvular stenosis as well as through the ventricular defect into the right ventricle and thence into the aorta The angiocardiographic findings are not in accordance with the diagnosis of Taussig Bing syndrome In this syndrome angiocardiographic studies as demonstrated by Martin and Lewis and by Kjellberg and associates[1] show that the root of the pulmonary artery is situated directly over the interventricular septal defect The aorta and the pulmonary artery are parallel in their origins the aorta is situated more laterally and arises only from the right ventricle and the pulmonary artery takes origin from both ventricles In our case as the angiocardiograms show the aorta is located anteriorly and laterally whereas the pulmonary artery is situated posteriorly (dorsally)

The extreme anterior position of the aorta as seen in the angiocardiograms is an unusual position according to the anatomic description given by Neufeld and associates[8] but does not exclude the diagnosis of origin of both great vessels from the right ventricle

In the double outlet right ventricle with pulmonary stenosis the functional alterations are superimposable upon those of classic tetralogy of Fallot When double outlet right ventricle is not accompanied by stenosis of the outflow tract the changes are similar to those found in cases of interventricular septal defect with pulmonary hypertension Although the case now reported should be included in the Fallot type complex those which are not accompanied by pulmonary stenosis should be included in the Eisenmenger type complex which are also rare. Neufeld and associates[11,12] and Cheng[4] have recently described some cases.

Summary

A case of double outlet right ventricle with pulmonary stenosis is described in which selective angiocardiographic findings established the correct diagnosis. The clinical electrocardiographic and radiologic data although slightly divergent are not sufficient to allow the differential diagnosis between this condition and classic tetralogy of Fallot.

According to the concept previously established by us this rare condition should be included in a seventh group of the Fallot type complex

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Experimental and laboratory reports

The vertical component of the heart vector

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It has been shown that the magnitude and direction of the horizontal component of the heart vector can be found from the measurement of many potentials over the thorax. For a cylindrical volume conductor the vertical component is found by integrations over the top and bottom surfaces. Thus

$$M_y = k \int\int V \, \underline{n} \, dx \, dz \tag{1}$$

M_y = component of dipole moment in vertical direction. If V is measured in mv., units of M are ma.-cm. k = average thorax tissue conductivity, ohm⁻¹ cm.⁻¹ V = potential at a each point on the surface. dx, dz = elements of distance in x and z directions.

Conventional axes are used in this paper, i.e., positive x, y, and z are toward the left, down, and back. The angle between the spatial vector and the horizontal plane is designated α, with positive values clockwise or downward from the plane. β is the angle which the projection of the vector on the horizontal plane makes with the +X axis. If the dipole moment M and the angles α and β are known, the dipole is completely determined.

Equation (1) cannot be applied rigorously to the human body since the head and extremities comprise very irregular top and bottom surfaces. The present paper describes a method for finding the vertical component based on Equation (1) which gives good agreement with artificial dipole results.

The vertical component of a dipole in a right cylinder

Theory. Equation (1) may be written

$$M_y = k \int\int V \, \underline{n} \, dx \, dz = k \int\int V \cos \gamma \, dx \, dz \tag{2}$$

In the general case the integrand is the product of the potential V and the unit normal vector n. The unit normal vector may be expressed as the cosine of the angle γ between the normal to the surface and the Y (vertical) axis, as shown in Fig. 1. For the top surface of a right cylinder γ = 0° and cos γ = 1, so that

$$M_y = k \int\int V \, dx \, dz \tag{3}$$

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The integration should be applied to both top and bottom surfaces. The mean potential in the top surface is given by

$$V_T = \frac{\int\int V_T \, dx \, dy}{A} \quad (4)$$

where A is the cross-sectional area. A similar equation holds for the bottom of the cylinder.

Substituting Equation (4) into Equation (3)

$$M = kAV \quad (5)$$

where V is the mean potential difference between the bottom and top surfaces, i.e.

$$V = V_B - V_T \quad (6)$$

Equation (5) has also been derived by Brody[2] using lead field theory. To our knowledge however this simple but very important equation has not been applied to the determination of the vertical component of the heart vector in living subjects.

Test of theory. In order to test Equations (3) and (5) artificial dipole experiments were carried out in two right cylinders of different cross sections and volumes. The first of these[3] had a cross section of an ellipse with major and minor axes of 32.1 and 25.7 cm. The depth was 43.6 cm. and the cross-sectional area was 698 cm.[2] The tank was filled with dilute NaCl solution of resistivity 1,020 ohm-cm. A Plexiglas sheet containing small holes spaced at 1-cm. intervals was placed on top of the tank. The dipole was energized with 1,000 c.p.s. alternating current, and the tank potentials were amplified and applied to a vacuum tube voltmeter as described previously. The dipole was located 13 cm. from the top and in the left anterior region of the tank. The dipole moment was 1.75 ma. × 1.40 cm. = 2.45 ma.-cm. The reference electrode was located at the bottom of the tank at the left side and an electrode at the bottom right side was grounded. A stainless steel tube with a platinum wire soldered to the end was placed through the holes in the top sheet until the liquid was contacted. Potentials were measured between this search probe and the reference electrode.

The potentials were measured in the x direction, i.e., in rows parallel to the frontal plane. For each row V was plotted against x, and the area under the curve was measured. These areas were then plotted as a function of z (directions parallel to sagittal plane) and the area under the resulting curve found. This value multiplied by the conductivity k gave the calculated value of the vertical component.

Three experiments were carried out with the dipole in the same position but making different angles with the horizontal plane. The results are shown in Table I. It is evident that there is a very good agreement, even though the variation of potential over the bottom of the tank was neglected. The dipole was 30.6 cm. from the bottom and only 13.0 cm. from the top so that the variation of potential of the bottom layer was small.

The second cylinder was made from plaster and was based on the dimensions of a dog on which the thorax potential distribution had been measured. This approximated an elliptical cylinder of mean cross-sectional area 164 cm.[2] although the neck and caudal regions were more nearly circular. The dipole was mounted vertically ($\alpha = 90°$) and was about 2.5

Table I. Comparison between values of M calculated from Equation (5) and experimental values for elliptical cylinder tank in ma.-cm.

α	M (exp.)	M (meas.)
85	2.43	2.42
45	1.73	1.71
0	0	−0.09

α = angle of dipole with horizontal plane. Experimental value of M = 2.45. M = M sin α.

cm. from the front wall The depth of fluid in the model was 56 cm and the dipole was at a depth of 20 cm The voltage was measured between the left leg electrode and an electrode suspended in the center of the neck region The dipole moment was 1 75 ma. times 1 40 cm pole separation = 2 45 ma.-cm V_y = 15.5 mv

From Equation (5) with $k = \frac{1}{1.036}$

$$M = kAV = \frac{164 \times 15.5}{1.036} = 2.45 \text{ ma-cm}$$

In a second experiment with the model the dipole was adjusted to make an angle of 45° with both the horizontal and frontal planes, i e. $\alpha = 45°$ $\beta = +45°$ The dipole location was the same In this case the potentials were measured with respect to a Wilson central terminal The experimental value of M was 1 73 ma.-cm. Using V equal to the left leg potential minus the potential of the top electrode M calculated = 1 62 ma.-cm Using the average of the center and four neck electrodes, the calculated value of M was 1 67 ma.-cm

The vertical component of a dipole in a human thorax model

The next group of experiments was designed to determine whether Equation (5) could be applied to the human body and to determine the accuracy of such measurements. For this and other artificial dipole experiments, an accurate, life-size Plexiglas model of the thorax was obtained (shown in Fig 2) The dimensions correspond to those of a young adult male the chest measurement is about 36 inches When the model was received the head was complete except for a hole in the top. A measurement with a vertical dipole showed that there was no potential variation in the head itself The head was removed above the chin to allow movement of the dipole.

Electrodes were installed on the chin and the limbs, as well as several rows around the thorax. Plastic pieces were cemented in place across the lower part of the junctions of the arms with the trunk in order to make the conditions more similar to those of the human body The dipole consisted of two silver plated brass balls with a center to-center spacing of 1 40 cm The dipole was accurately adjustable between α angles of 0° to 90° by means of a knob and multi turn calibrated dial on top of the vertical support rod

Determination of V_y. Two equations for the average vertical potential difference V were tested The first of these was the left leg -head lead

$$V = V - V \qquad (7)$$

The second was an equation developed from Simpson s rule which is a method of finding the approximate area under a curve.* The potentials of the right arm head and left arm are plotted against distance The ordinates are separated by a distance d. Using Simpson s three-ordinate rule, the area under the curve connecting the points is

$$A = \frac{d}{3}(V + 4V_H + V) \qquad (8)$$

The mean potential is found by dividing this area by 2d Hence,

$$V = \frac{V + 4V_H + V}{6} \qquad (9)$$

Subtracting this from the left leg potential and converting to bipolar form this becomes

$$V = \frac{II + III + 4(V - V_H)}{6} \qquad (10)$$

*Obtained from Deutsches Gesundheits-Museum, Ostmerheimer Strasse 200, Köln-Merheim, Germany

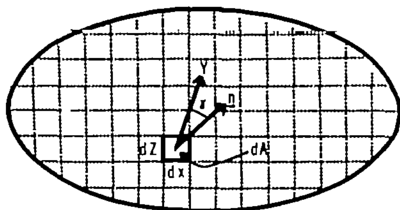


Fig. 1. Method of finding vertical component of heart vector M_y. The element of area is the rectangle dA, with sides dz and dx. n is unit vector normal to the surface, and Y is vector parallel to the y coordinate axis. The spatial angle between these vectors is γ. The potential V is multiplied by cos γ and dA, as given in Equation (2), and this product is integrated over the surface. For the top and bottom surfaces of a right cylinder γ = 0°.

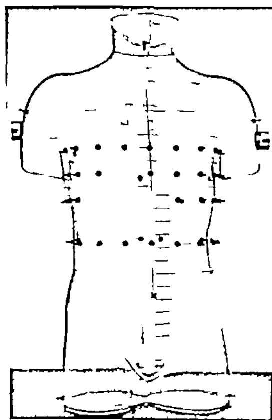


Fig. 2. Plexiglas thorax model. The electrodes were machined from brass rod. The disks are 1 cm. diameter and 1 mm. thick, and are silver plated. A rubber grommet cut in half was placed between the disk and the wall to prevent the leakage of fluid.

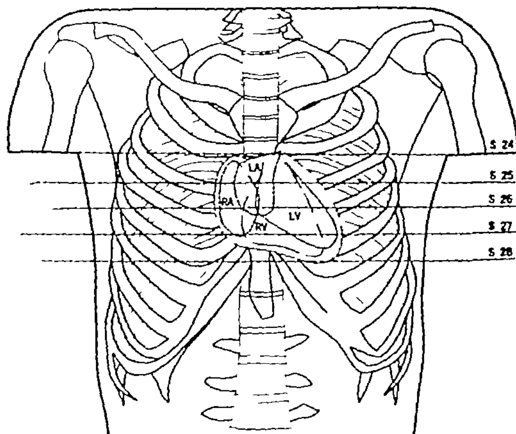


Fig. 3-6 Drawings used to specify coordinates of dipole location. (Adapted from *A Cross-Section Anatomy* by Albert C. Eycleshymer and Daniel M. Schoemaker 1938 by permission of Appleton-Century-Crofts.) The sections or levels have the same numbers used in the book. x = 0 is at the mid-sternal line = 0 was taken at the seam where the two halves of the model were joined at fabrication and does not represent an anatomic location. The oval in the cross sections represents the neck opening. The vertical sections are one inch apart. (For Figs. 4, 5 and 6 see opposite page.)

It was thought that this equation might compensate for changes in position of the dipole because it brings in the potentials of the left arm and right arm. Subsequent data will show, however, that Equation (7) gives about the same results as Equation (10) and is simpler.

Specification of dipole locations. Because we wished to study the effect of the location of the dipole on the vertical component, it was necessary to adopt a coordinate system by which the dipole position could be specified. Drawings were made of cross sections through the thorax based on illustrations in an anatomy textbook.[6] The sections used were 25 through 28. The drawings based on these sections are shown in Figs. 3 through 6. In the measurements, the dipole was moved through a range of values of x, y, z to more than encompass the heart volume shown. This was done in order to take into account individual variations in heart size, shape, and position.

Value of area A. Since the cross section of the human thorax is not uniform, the question arises as to what value to use for A. This choice is important because it directly affects the magnitude of the calculated vertical component, as shown in Equation (5). The area was determined as a function of depth by filling the model with water and siphoning off through successive 2-cm. intervals. Dividing the volume of water removed by 2 cm. gave the average area in that interval. The average value of A for the entire model was 616 cm.[2] and the average thorax cross-sectional area was 586 cm.[2] Accordingly, a value of 600 cm.[2] was used for A for this model.

to the latter it is known that excessive carbohydrate inhibits the excretion of sodium.[22] By administering glucose I have been able to dramatically reproduce within 1 day the edema of several women who were subject to recurrent edema and hypoglycemia.[23] Furthermore I have observed rises in the serum sodium—albeit transient and slight—in 4 such patients whose levels of serum sodium were determined hourly after glucose loading.[23] For example, the fasting level of serum sodium of 139 mEq L. in Case 20 rose to 142 mEq L. 1 hour after glucose loading.

The benefits of a low-fat dietary intake in cardiac patients are suggested by the following recent observations. (1) Over 50 per cent of patients with gross evidence of right-sided heart failure may have impairment of fat absorption (as demonstrable by radioactive-iodinated triolein studies), the degree of malabsorption being related to the severity of the decompensation.[23] (2) A digestive defect (as indicated by marked impairment of I[131]-oleic acid absorption) also may exist presumably the result of congestion and edema of the pancreatic acini and intestinal mucosa.[24] (3) There is usually a persistent elevation of the serum triglycerides during milk cream feedings for peptic ulcer, such hyperlipemia being further exaggerated when a lipid disturbance already exists.[25] (4) The degree of impairment of radioactive fat tolerance likewise is abnormal, and tends to be proportional to the height of the triglyceride concentration. (5) Acceleration of thromboplastin evolution appears to be dependent not only on the degree of lipemia, but also on the type of fat ingested. In one such study[24] it was shown that the greatest acceleration of thromboplastin generation followed the alimentary lipemia that occurred after the ingestion of butter, whereas only slightly accelerated evolution followed the ingestion of liquid corn oil.

Following the initial rapid reduction in weight due to both a diuresis and loss of fat after the ingestion of a hypocaloric and sodium-poor formula diet, loss of weight tends to occur at a more steady (albeit less dramatic) rate. Because of compensatory adjustments by the body (largely related to retention of fluid) this reduction in weight may not assume the form of a line when depicted on a weight reduction graph. In view of the restricted activity required of most patients who have active or recent congestive failure, this dietary program has provided an eminently helpful means of reducing weight when their caloric expenditure could not be safely increased.

I have consistently observed that obese patients with congestive failure and other cardiac disorders generally have at least two other conditions which are concomitantly benefited by a significant reduction in weight. These include essential hypertension, recent or previous thrombophlebitis, the postphlebitic syndrome, arteriosclerotic peripheral vascular disease, angina pectoris, paroxysmal rapid heart action, hypercholesterolemia, diabetes mellitus, gall-bladder disease, gout, osteoarthritis of the weight-bearing joints, and narcolepsy associated with recurrent hypoglycemia (currently referred to as the Pickwickian syndrome).[22,27] A striking example of this experience was posed by one patient (Case 9) in whom eight disorders (viz., thrombophlebitis, pulmonary embolism, angina pectoris, congestive heart failure, diverticulitis, episodic vertigo, and recurrent hypoglycemia and a peripheral neuropathy symptomatic of diabetes mellitus) existed concomitantly or consecutively—each condition requiring consideration in his general medical and dietetic management. The importance of recognizing and treating concomitant narcolepsy in obese patients who are experiencing recurrent hypoglycemia has been emphasized if a reducing program is to be successful.[22,27] Methylphenidate hydrochloride (Ritalin) in doses of 2.5 to 10 *mg.* twice daily has proved to be most satisfactory in this regard because of the relative absence of sympathomimetic side reactions.

It has been demonstrated that a significant decrease in the level of serum cholesterol consistently accompanies a formula-induced reduction in weight in hypercholesterolemic patients. Anticoagulant escape (as evidenced either by significant prolongation of the prothrombin time or clinical bleeding) has not been encountered during such a program in patients who

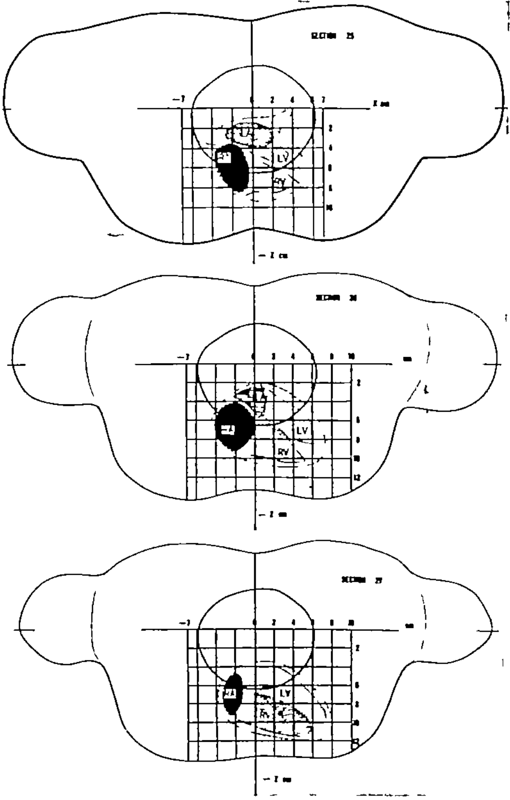


Fig 4 (*top*), Fig 5 (*center*), and Fig 6 (*bottom*). For legend see opposite page.

In practice the area can be estimated from the anterior posterior and the lateral chest measurements by assuming an elliptical cross section. The area of an ellipse is

$$A = \frac{\pi ab}{4} = 0.79\,ab \cong 0.8\,ab \tag{11}$$

where a and b are the *total* major and minor axes.

Conductivity k. Although it has been shown[4,7] that the intracardiac blood may have a significant effect upon the electrocardiogram, this factor is at present neglected. The value k therefore represents the average conductivity of the body. In the model experiments the resistivity of the fluid was adjusted to be about 500 ohm.-cm. It was thought to be worth while to study first the homogeneous case. The effects of variations of resistivity can then be introduced as correction factors.

Effect of the angle β. In this experiment, the dipole was placed successively in four locations corresponding approximately to the four heart chambers. At each location values of $\alpha = 90°$, $60°$, $30°$, $0°$, $-30°$, and $-60°$ were used. For each value of α, measurements of the limb leads and the foot head lead were made for values of β from $+90°$ to $-60°$ at $30°$ intervals. These experimental values covered one hemisphere; the values for the opposite angles were obtained by assuming a reversed polarity of the dipole.

Equation (5) was in good agreement with the experimental results for different values of α when β was $0°$ or $\pm180°$. For $\beta = \pm90°$ there was a considerable variation from the calculated values. It was found that the deviations from the correct values were approximately sinusoidal functions of β. Fig. 7 shows the average curves for the four dipole locations together with sine curves having the same relative amplitudes. The magnitudes have been standardized to correspond to a total dipole moment of 1.0. This was done by dividing the measured lead potentials by the actual dipole moment. The units of potential are therefore in mv. ma.-cm.

These curves show that the peaks of the sine waves are smaller for larger values of α. For $\alpha = 90°$, i.e., a vertical dipole, the angle β does not enter, and the calculated value of kAV is a straight line near 1.00. The peak of the error curve, therefore, approaches zero as $\alpha \rightarrow \pm90°$. The results for $\alpha = -30°$ and $-60°$ were similar to those for the positive values, except for polarity. The same wave shape occurred, however, i.e., for α negative values of kAV for positive values of β were larger than those for negative values of β.

The curves for the individual dipole locations showed similar sinusoidal variations with β. The peak deviations were greater for the auricular than for the ventricular locations.

Modified equation for M_y. In the light of this experiment, a correction factor of K cos α sin β was tried. For $\alpha = 0°$ this would be a maximum for $\beta = \pm90°$. The value of K is, therefore, equal to kAV when $\alpha = 0°$ and $\beta = -90°$. For $\beta = 0°$ or $180°$ the correction is zero. Also as α goes from $0°$ to $\pm90°$ the correction factor decreases.

If the actual value of M is used, the factor becomes $KM \cos\alpha \sin\beta = KM_z$. Therefore Equation (5) becomes

$$M = kAV + KM_z \tag{12}$$

K is an empirical constant which must be determined from experiments.

Measurement of M as a function of dipole location. The dipole support was mounted on a sliding bar assembly so that it could be moved in the x direction, i.e., parallel to the frontal plane. For various values of z, the dipole was moved between the minimum and maximum values of X which could be physically reached. At each point the foot head lead and the limb leads were measured for $\alpha = 0°$, $45°$, and $90°$ and $\beta = 0°$, $45°$, and $90°$ for each value of α. This was done for each of levels 25, 26, 27, and 28.

The results for $\beta = 0°$ and level 26 are shown in Fig. 8. With $\alpha = 0°$ the x position of the dipole has little effect. There is a small change with X. The maximum value of kAV is $-.07$. With $\alpha = 45°$ the effect of z is much greater. The correct value of M is 0.71, as shown by the horizontal line. The X position of the dipole has relatively little effect.

With $\alpha = 90°$ the changes in kAV with z are much larger than the changes with

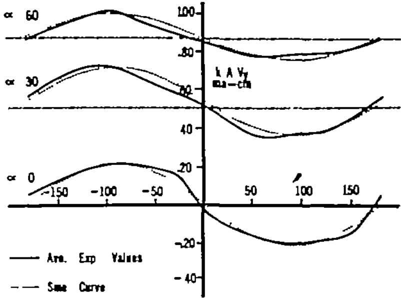


Fig. 7 Average measured values of kA(V F-V) as function of β for four dipole locations. The ordinates are standardized, i.e., the values are those which would be obtained if the dipole had total moment of 1.0 ma.-cm. The dotted curves are sine wa es drawn to coincide as closely as possible.

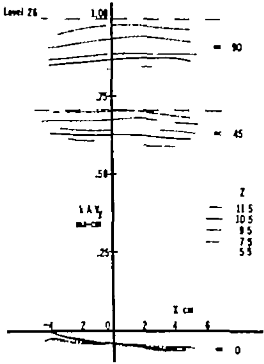


Fig 8 Measured alues of kA(V F-V H) as function of the X location of the dipole for arious positions. Level = 26 The dipole is parallel to the frontal plane, i.e., β = 0°

Table II Values of kAV for β = 0° in ma.-cm.

Lead		Number of observations	V from Simpson's rule					V = V − V_H				
			Min.	Max.	Range	Mean	S.D	Min.	Max.	Range	Mean	S.D
25	0	25	03	− 07	10	− 023	030	− 01	− 04	03	− 023	012
	45	25	55	68	13	623	034	61	75	14	686	039
	90	25	80	93	13	872	042	85	1 04	16	964	032
26	0	35	03	− 11	14	− 046	042	− 01	− 07	06	− 044	016
	45	35	54	69	15	620	038	60	71	11	661	036
	90	35	78	93	15	857	046	83	1 00	17	912	052
27	0	36	04	− 10	14	− 037	044	01	− 07	08	− 038	024
	45	36	59	71	12	641	035	61	71	10	667	030
	90	36	82	96	14	893	040	86	99	13	928	042
28	0	36	04	− 09	13	− 032	039	02	− 07	09	− 033	027
	45	36	61	72	11	668	032	63	73	10	687	030
	90	36	87	98	11	922	037	89	1 01	12	946	037
All levels	0	132	04	− 11	15	− 035	041	01	− 07	08	− 035	023
	45	132	54	72	16	639	040	60	75	15	674	036
	90	132	78	98	20	888	048	83	1 04	21	936	050

Table III Anatomic location of dipole for data of Table IV

Position	Location	Level	Y	−Z
1	Center of right atrial cavity	Between 25 and 26	−2	6 25
2	Sinoauricular node	25	−4	5
3	Anterior wall of right auricle	26	−3	9 5
4	Center of left atrial cavity	Between 25 and 26	−0 4	3 5
5	Lateral wall of left atrium	25	2	3
6	Center of posterior wall of left atrium	Between 25 and 26	−0 4	2
7	Central portion of interventricular septum	Between 26 and 27	3 5	9
8	Apex	28	8	11
9	Center of anterior wall of right ventricle	Between 26 and 27	2 5	11
10	Center of lateral wall of left ventricle	Between 26 and 27	7 5	7
11	Posterobasal portion of left ventricle	Between 27 and 28	2	4

N. Also the changes with z are greater than for $\alpha = 45°$. As the dipole is moved closer to the front wall, i.e., z is made larger, the measured values of kAV become smaller.

In Fig. 8 no correction for M is needed since $\beta = 0°$. All the changes for a given value of α are due solely to changes in dipole location. If the dipole is at the assumed center of the heart, i.e., level 26, $N = 1.5$, $z = -6.5$, the calculated value of M for $\alpha = 90°$ is 0.97 as compared to a true value of 1.0.

Table II shows the minimum and maximum values of the calculated values of M using Equation (5). In addition, the ranges, mean values, and standard deviations are shown for each value of level and angle α. Columns 4 to 8 are based on the determination of V by Simpson's rule, Equation (10). Columns 9 to 13 were calculated using the foot head lead for V. In determining the standard deviations the data were treated as if they were purely random. Table II therefore shows the errors involved if the dipole location is ignored

Comparing columns 7 and 12 shows that in general the mean values computed using Simpson's rule for V are smaller than the means computed using the foot-head lead This could be corrected by using a somewhat larger value of the thorax cross-sectional area A in Equation (5) The ranges and standard deviations are about the same, however so that there is no advantage in using Equation (10) Equation (5) in fact gives closer results to th true values of M = 0 0 71 and 1 00 when the actual cross-sectional area is used

The results for $\beta = 45°$ were similar to those of Fig 8, except that they were displaced in magnitude in agreement with Fig 7 For $\alpha = 0°$ all values were more negative and for $\alpha = 45°$ all values were less positive than in Fig 8 The variations with x and z changes of the dipole were similar The value of kAV at the heart center was 0 63 For $\beta = 90°$ the displacement of the curves was still greater The value at the heart center was 0.57

For other values of β the variations would be different and would follow Fig 7 The data in these tables were not corrected by using the factor KM of Equation (12)

Values of M with the dipole at selected regions of the heart In order to study the effect of changes of location of the dipole within the heart volume M was measured with the dipole placed at 11 different positions, as shown in Table III The results are shown in Table IV

At each location measurements of the foot head lead were made with dipole angles of $\alpha = 0°$ 45° and 90° and $\beta = 0°$ 45° and 90° The first column in each position gives values of kAV using k = 1/500 and A = 600 cm The next column gives KM_z, and the results in the last column are equal to the values of the first column plus those of the second column. Experimental values of α, β M_y, and M are listed at the left.

Comparison of the experimental and measured values of M shows the improvement brought about through use of the correction factor KM The table shows that for the 11 locations chosen K varied from 10 at the apex of the heart to 21 in the right auricle near the sinoauricular node. The average value of K for the 11 positions was 16. The data for

Table IV Values of M with dipole at selected positions

α	β	M (exp)	M	kAV	KM_z	M (meas.)	kAV	KM_z	M (meas.)	kAV	KM_z	M (meas.)	kAV	KM_z	M (meas.)
				Position 1 K = 18			Position 2 K = 21			Position 3 K = 15			Position 4 K = 16		
0	0	0	0	−.04	0	−.04	−.04	0	−.04	−.02	0	−.02	−.04	0	−.04
	45	0	71	−13	13	0	15	15	0	−13	11	−.02	−.07	11	.04
	90	0	1 00	−18	18	0	−.21	21	0	15	15	0	−16	16	0
45	0	71	0	70	0	0	70	0	70	.65	0	63	72	0	72
	45	71	50	.63	.09	72	63	11	74	58	08	66	65	.08	73
	90	71	71	.56	13	.69	.57	15	72	50	11	61	62	11	73
90		1 00	0	97	0	97	99	0	99	88	0	.88	1 02	0	1.02
				Position 5 K = 17			Position 6 K = 16			Position 7 K = 16			Position 8 K = 10		
0	0	0	0	−01	0	−.01	−.04	0	−04	−.06	0	−06	−.08	0	−.08
	45	0	71	−.05	12	.07	−.07	11	.04	15	11	−04	−10	.07	−.03
	90	0	1.00	−17	17	0	−16	16	0	16	16	0	−10	10	0
45	0	71	0	76	0	76	72	0	72	65	0	.63	.63	0	63
	45	71	.50	.67	.09	76	65	.08	73	.59	.08	.67	62	.05	67
	90	71	71	.63	12	75	.62	11	73	54	11	.65	.65	.07	72
90		1.00	0	1.04	0	1.04	1 02	0	1 02	90	0	90	92	0	.92
				Position 9 K = 16			Position 10 K = 15			Position 11 K = 15					
0	0	0	0	−06	0	−06	−.07	0	−.07	−05	0	−.05			
	45	0	71	−15	11	−.04	−14	11	−03	−.09	11	.02			
	90	0	1.00	−16	16	0	−15	15	0	−15	15	0			
45	0	71	0	62	0	.62	.67	0	67	71	0	71			
	45	71	50	.55	08	.63	.59	.08	67	.64	.08	72			
	90	71	71	52	11	.63	.56	11	67	63	11	74			
90		1.00	0	.88	0	.88	95	0	95	1 00	0	1.00			

Table V. Magnitude of heart vector components for W. M. in ma.-cm.

Time msec	M	M	M	α	kAV	M	α	15M	Corrected values M	Corrected values M	Corrected values α
5	−8	242	250	−103	−314	400	−51	−36	−350	430	−54
10	−48	−476	478	−96	−324	578	−34	−72	−396	620	−40
15	130	−08	720	−60	−232	756	−18	−106	−338	796	−25
20	278	736	786	−69	34	786	2	−110	−76	790	−6
25	00	−596	920	−40	568	1 080	32	−90	478	1 036	27
30	8[illegible]4	−368	902	−24	1 426	1 688	58	−56	1 370	1 640	37
35	962	26	962	2	2 4 0	2 650	69	4	2 474	2 654	69
40	1 038	6[illegible]6	1 228	32	2 866	3 120	67	98	2 964	3 208	67
45	418	924	1 014	66	2 076	2 410	64	138	2 214	2 436	65
50	−1[illegible]8	1 096	1 108	98	1 252	1 672	48	164	1 416	1 798	52
55	−436	664	794	123	488	932	32	100	588	988	37
60	42[illegible]	462	626	132	−44	626	−4	70	26	626	2
6	−408	360	544	138	−324	634	−31	54	−270	608	−26
0	−30[illegible]	272	408	139	−430	594	−47	40	−390	564	−44
5	−230	150	274	146	−360	432	−53	22	−338	436	−51
8[illegible]	−1 2	10[illegible]	202	148	−314	374	−57	16	−298	360	−56

complete x z scanning showed that the maximum variation in K for all levels was from 09 to 24 or a range of 15

The effect of changes in location of a vertical dipole on M calculated by Equation (5) can be seen by comparing the values for $\alpha = 90°$ in Table IV. At position 3, at the anterior wall of the right auricle and at position 9 at the center of the anterior wall of the right ventricle M = 0 88 ma.-cm. At position 5 on the lateral wall of the left auricle, M = 1 04 ma.-cm. Thus changes in location can cause about a 16 per cent change in the observed value of the vertical component in a medium-sized heart.

From the data of Table IV the average value of K for the right auricle (positions 1 3) is 18 for the left auricle (positions 4-6) the septum (position 7) and the right ventricle (position 9) it is 16 and for the left ventricle (positions 8 10 and 11) it is 13

Since the mean value of K for levels 25 to 28 is 144 and since these data cover a wider range of dipole locations than Table IV an average value of K = 0.15 was used. Then if the location of the dipole is ignored equation (12) becomes

$$M = kAV + 0.15 M \qquad (13)$$

Vector lead for the vertical component

Equation (13) can be used as the basis of a vector lead system for the vertical component, using analog computer concepts. The foot head lead ($V_F - V_H$) must be multiplied electrically by kA with a potentiometer adjustment in the circuit to take care of variations in this factor. This resulting voltage must then be added to 0.15 M_x. A voltage divider can be applied across the lead system used to measure M in order to multiply this value by 0 15.

The value of M in Equation (13) is the z component of the actual dipole moment of the heart vector. The factor of proportionality between M and the z lead must therefore be known

Magnitude of the spatial heart vector for the human being

Table V shows the values of M, M_x, kAV, 15M_x, and M for a young adult male. M and M were determined from thorax integrations using 8 levels of 20 electrodes around the thorax. The potential distributions were measured at 1 millisecond intervals using a

scanning device previously described.[9] The values of M α and β completely determine the spatial dipole.

The effect of the correction factor 15M can be seen by comparing the values of kAV with M In the table columns 7 and 8 give values of M and α computed using the values of kAV Columns 11 and 12 give the values of M and α after correction was made. The area A was taken as the average value for the third to sixth intercostal spaces, and was equal to 580 cm.[2] The conductivity k was assumed to be 002 ohm^{-1} cm. or ρ = 500 ohm-cm This value of the mean thorax resistivity is based on the measurements of Schmitt[11] and Burger and van Dongen.[12] According to Pozzi,[13] Burger and Schwann have agreed that the specific resistance of the whole body is about 500 to 600 ohm-cm Since the dipole components are directly proportional to conductivity k, the effect of using k = 002 instead of 001 as we have done in the past[1] is to double the values of the dipole moments. Table V shows that the peak value of M for W M is 3 2 ma.-cm.

It is evident that for this subject the magnitude and direction of the spatial vector M were not greatly changed by the correction factor KM. The maximum change in α was 8° and in M about 8 per cent. For a more horizontal heart, however the change might be greater The change in M itself was more marked, but when M was combined with M and M the over all effect is diminished. The magnitudes of M and M were accurately known in this case. If errors existed in the measurement of the horizontal components, these errors would add to those in finding M when determining the spatial vector

The frontal and sagittal loops can be obtained from Table V by means of the following equations

Frontal

$$M_f = \sqrt{M^2 + M^2} \tag{14}$$

$$\tan \alpha_f = \frac{\tan \alpha}{\cos \beta} \tag{15}$$

Sagittal

$$M = \sqrt{M^2 + M^2} \tag{16}$$

$$\tan \alpha = \frac{\tan \alpha}{\sin \beta} \tag{17}$$

where M_f and M are the projections of M on the frontal and sagittal planes, and α and a are the angles to these projections in the planes. Values of M_h and β are available in the table, for the horizontal loop. These loops are shown in Fig 9

Discussion

It should be emphasized that Equation (13) gives the absolute value of the vertical component, subject to the errors involved in assuming a homogeneous thorax, the accuracy of determination of A and k, and in neglecting changes in dipole position Also the possible effects of multipole components on the foot head lead are neglected. Even though these errors may be considerable the equation at least serves as a first approximation to the magnitude of the vertical component. It would seem worth while to determine the correct values for a single dipole in the homogeneous thorax as a starting point for further developments.

The values of M and M determined from thorax integrations are also correct in absolute magnitude subject to similar considerations. These equations give the value of the *resultant* dipole moment Local variations in chest potentials tend to be averaged out by the integration process.

Equation (12) shows that M is not necessarily zero when V is zero At this time

$$M = KM \tag{18}$$

and is not zero unless M is also zero

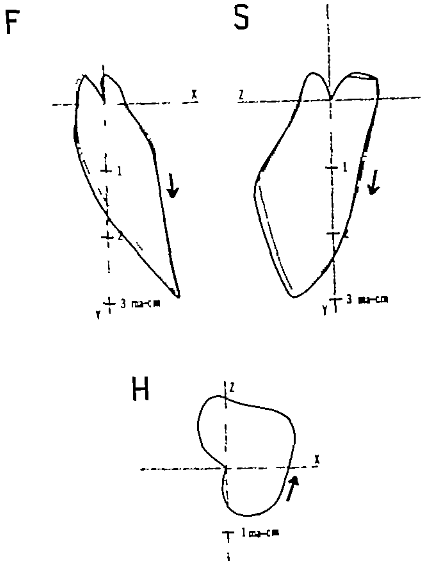


Fig 9 Vector loops for W M young adult male. Scale represent actual values of dipole moment in ma.-cm., assuming homogeneous thorax of mean resistivity 500 ohm-cm. The loops are shown both with (*solid line*) and without (*broken l*) correction for sagittal component in foot-head lead.

The fact that the z component of the dipole contributes to the foot head lead is due to the boundary effect i.e the distortion of the current field caused by the shape of the thorax. Examination of Fig 8 shows that M also contributes a small amount to V $_F$ V $_R$ When $\alpha = 0°$ and $\beta = 0°$ M should be equal to zero The finite values of M shown are due to the X component of the l pole only Table II shows that the range of kAV due to M is only from 01 to − 07 ma -cm for all dipole locations, and that the mean values for the 4 levels range from − 02 to − 04

Several investigators[1-17] have used the left leg to head or left leg to neck for the vertical component Frank and Helm have compensated for the sagittal component by using resistance networks between the left leg and a point on the back. Preliminary tests with our thorax model indicate that Frank s back lead is too close to the heart and overcompensation results for some dipole locations. Helm s back lead is at a lower level and corrects in the right way but not quite enough Also in both systems the vertical lead is affected by the

potential of the back electrode when the dipole is vertical although the Helm lead is no seriously changed.

It would seem that somewhat better compensation could be achieved by combining the foot-head lead with a bipolar lead at a fairly low level across the thorax approximately parallel to the sagittal plane. Such a bipolar lead should not be greatly affected by the left right or vertical components of the dipole for various dipole positions. The location of these electrodes must be found from additional model measurements.

The heart position shown in Figs. 3 through 6 is not, of course applicable to all indi viduals. The object of this investigation was to show relative changes in the vertical lead which might be caused by a dipole moving throughout the heart volume. The results show that a correction factor K, can be assigned to each of the heart regions. The accuracy of Equation (12) could be increased by using the value of K applicable to the particular de flection being studied

Schmitt found considerable variation between individuals with regard to average chest resistivity but gives a mean value of 489 ohm-cm. at mid-respiration. His data show a correlation of $r = +0.61$ between resistivity and cross-sectional area, with ρ higher for larger individuals. This would mean that the product KA in our equations might tend to remain constant.

Equation (12) can be rewritten to correspond to the lead vector equations of Burger and Van Milaan who show that for any lead (in our notation)

$$I = a\,M + b\,M + c\,M \qquad (19)$$

Solving Equation (12) for V

$$I = \frac{\rho}{A} M - K\frac{\rho}{A} M \qquad (20)$$

If the correction for M is also used and letting K = 0 15 this becomes

$$I_F - I_H = \frac{\rho}{A}(-.035M + M - 15M) \qquad (21)$$

Equation (21) shows that the left leg to-head lead is made up of 3.5 per cent of M M and 15 per cent of M all multiplied by average thorax resistivity divided by cross-sectional area The equation gives an average value for 11 d pole positions in the heart volume and should be applicable to any individual provided that the appropriate values of ρ and A are used As stated previously other factors such as the intracardiac blood may affect the results.

Fig 8 shows that when $\alpha = 90°$ measured values of kAV are lowest to the correct value of 1 00 when $x = -5\ 5$ cm This represents a region about 1 cm. posterior to our assumed heart center and is closest to the center plane of the thorax model, at $Z = -3\ 0$ of any of the curves For d pole positions closer to the anterior wall the measured value d creases. A similar situation exists in Table IV although the X and level positions also affect the results somewhat. Table II shows that the mean value for all levels is 0 94 The mean value for $\alpha = 90°$ n Table IV is 0 96. Using an over all aver ge of 0 95 Equations (5) (12) (13) and (21) can be modified to give better average values for all dipole locations studied. This is done by mult pl ng KAV by $\frac{1}{.95} = 1\ 05$ In th s case Equation (21) becomes

$$I - I = \frac{\rho}{A}(-.033M + .95M - 14M) \qquad (2\ )$$

If we had used the average area of the entir torso 616 mstea l of 600 m the results would have been somewhat closer to the over-all average values

The concept of the determination of the dipole moment f om mea top and bottom

Helm has informed us that he has recently used back electrode his vertical lead

surface potentials on a right cylinder has been illustrated by McFee and Johnston[19] on the basis of their lead field studies.

Summary

When a dipole is immersed in a homogeneous right cylinder of arbitrary cross section the vertical component is equal to kAV where k is the conductivity, A is the cross-sectional area, and V is the mean potential difference between bottom and top surfaces. By means of experiments in an accurate life-size Plexiglas thorax model it was shown that this equation is valid when using the left leg-to-head lead for V, provided that a certain fraction of the sagittal component of the dipole moment is added to $V_F - V_H$. For 11 representative dipole locations in the heart volume this ratio K_s is 0.15 on the average.

A new system of measuring the mean vertical voltage was tested but was found to have no advantage over the simple foot-head lead. Changes in dipole location in a medium-sized heart can cause changes in the observed value of the vertical component of up to 16 per cent. Changes of location in the sagittal direction have much more effect than shifts parallel to the frontal plane. A generalized Burger equation for the foot-head lead was derived with the factor resistivity divided by area common to all three vector components. A vector lead for the vertical component is proposed. Absolute magnitudes and directions of the spatial vector for one individual are given on the assumption of a homogeneous thorax of mean resistivity equal to 500 ohm-cm. The peak value of the depolarization moment was 3.2 ma.-cm.

We wish to acknowledge the valuable assistance of Arthur Wilkinson and Paul Gastonguay in this project.

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are being concomitantly maintained on long term anticoagulant therapy.[7,8]

There is ample evidence that well conceived formula diets of which Metrecal is a prototype offer a significant methodologic advantage in the management of well motivated obese patients.[7,8,23] When such a regimen is integrated into the physician's necessarily multifaceted approach to the complex problem of effective long term weight reduction the criticisms of nutritional hazard economic exploitation and food faddism are not justified. The practicality and palatability of such formulas their relatively low cost the elimination of guesswork, recent improvements in their physical composition and variations in flavor and form to minimize monotony have facilitated the initiation and maintenance of weight reduction when this approach is indicated. On the other hand the physician is not freed from the responsibility of adequately indoctrinating his patients in proper dietotherapy and other aspects of proved value in getting patients to lose weight especially personal counsel and an adequate program of activity.

Finally the present study further underscores the need for recognizing that a useful life is subsequently possible in cardiac patients who have suffered heart failure. If the condition is promptly corrected many such individuals may regain considerable functional capacity with which productive work can be safely performed. For example in one series of 71 patients with congestive failure who were observed at the Seattle Cardiac Work Evaluation Clinic, 38 per cent were able to resume employment without serious consequences.[29] In this series an 80-year-old insurance executive (Case 17) was able to resume his occupation shortly after his myocardial competency had been improved.

Summary

A food formula (Metrecal) has been successfully employed as the sole or major source of sodium and calories in the management of 17 patients with congestive heart failure and 3 patients with lymphedema. This preparation supplies 900 mg. of sodium 70 Gm. of protein and 900 calories per quart. Obesity was not a factor in 11 of these individuals. Gratifying diuresis in a patient with anasarca due to carcinomatosis also is cited.

The advantages of this diet over other low-sodium regimens—with particular reference to the standard or modified Karell diet and the rice diet—include the following: (1) its palatability acceptability convenience and relatively low cost (2) the insuring of an adequate intake of protein calories vitamins, and minerals (3) the minimizing of postdiuretic asthenia (4) the frequent reduction in oral and parenteral diuretic requirements (5) the high buffering capacity against gastric acidity (6) the minimizing of hypoglycemia and edema that can occur after excessive ingestion of carbohydrate in patients who are subject to recurrent hypoglycemia (7) the absence of anticoagulant escape in patients being concomitantly maintained on long term anticoagulant therapy (8) its effectiveness as an outpatient dietetic regimen—in conjunction with digitalis diuretic agents local treatment to the lower limbs and other standard measures—in preventing hospitalization (9) the significant reduction in hypercholesterolemia and (10) its effectiveness in initiating long term weight reduction when the patient is obese as well as edematous. The last feature is especially advantageous in those cardiac patients whose caloric expenditure cannot be safely increased by exercise.

In several patients a significant diuresis was induced after digitalis oral and parenteral diuretics adrenocortical steroids, and even spironolactone had failed to reduce edema. In 4 patients it was not necessary to resort to spironolactone when its use was being contemplated because of a prompt diuresis after treatment with the sodium poor formula. Two patients with anasarca appeared to have a potentiated diuretic response when the formula diet and spironolactone were administered together.

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The apexcardiogram in normal older subjects and in patients with arteriosclerotic heart disease Effect of exercise on the 'a' wave

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We previously reported [4] abnormalities of the apexcardiogram (ACG) at rest and after exercise in patients with arteriosclerotic heart disease (ASHD) Because abnormal ballistocardiograms have been described in "normal older subjects without clinical evidence of ischemic heart disease t was necessary to investigate whether these changes in the ACG could occur merely as a result of aging

The purpose of this work is to study the ACG at rest and after exercise in normal older subjects, and to compare this data with abnormalities seen in patients with ASHD [4]

Material

Group I Sixty four consecutive normal subjects who ranged in age from 40 to 84 years (average age 54.6 years) were studied. There were 40 men and 24 women The criteria used for the selection of the patient material were (1) complete negative history of heart disease, (2) normal physical examination of the cardiovascular system and (3) normal electrocardiograms.

Group II Forty five consecutive patients with ASHD who ranged in age from 37 to 79 years (average age 60 8 years) were studied. There were 37 men and 8 women The criteria used for the selection of patients were (1) documented clinical and laboratory evidence of an old myocardial infarction (MI) (2) typical history of angina pectoris (AP) with or without an old MI and (3) atypical history of AP or no AP but with unquestionably abnormal electrocardiogram (ECG) at rest or after exercise compatible with myocardial ischemia (inversion of the T waves nversion of the U waves, and depression of the S-T segment)

One or more of the above-mentioned criteria were present in each subject. Blood pressures were normal in the subjects of both groups.

The patients with ASHD were further subdivided thus Group A—3 patients with definite history of MI without AP Group B—9 patients with AP no MI Group C—16 patients with MI and AP Group D—17 patients without MI or AP with abnormal ECG at rest or after exercise in the absence of any valvular disease or primary myocardiopathy For the purpose of this study the ECG was

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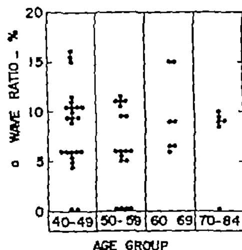


Fig. 1. Frequency distribution of the wave ratio of the ACG at rest in 64 normal subjects in different age groups. Note that all subjects had this ratio below 20 per cent. There was no significant increase in this ratio in the older decades. See text.

considered to be abnormal when ischemic changes were present, i.e. deep cove plane T waves in several leads and especially in Leads I, aVL, V, V, and V associated with S-T segment depression of no less than 2 mm. These changes were present at rest in all 17 patients and were accentuated after exercise (Class IV positive response to exercise according to Dimond's classification.) Digitalis was not an explanation for these electrocardiographic changes, since none of these patients was receiving any.

The degree of exercise was that of the double Master's two-step test which was used in all subjects except those who underwent cardiac catheterization and determination of cardiac output; the latter performed exercise on a calibrated bicycle. The ACG was recorded in all patients prior to, immediately after, and every minute after exercise for 10 minutes. One patient underwent right heart catheterization and a second left heart catheterization.

Cardiac output was determined in 7 ASHD patients at rest and during and after exercise using the indicator-dilution technique (indocyanine Cardio-green).

Method

Recording equipment for the ACG of the left ventricle consisted of the multichannel Electronics for Medicine DR-8 oscilloscopic photographic recorder and a pulse wave crystal microphone (Sanborn No. 374). A medium frequency phonocardiogram (40 to 200 cycles per second) at the mitral area and Lead II of the ECG were recorded simultaneously with the ACG in all subjects at a speed of 75

*Hynson, Westcott and Dunning, Inc., Baltimore, Md.

Table I. Apexcardiogram in normal subjects and in patients with ASHD. Range and averages of the a wave ratio, its duration, a-E interval, and rapid filling wave (RFW) ratio at rest and after exercise (see text)

	Time	Ratio Range (%)	Ratio Average (%)	a Duration Range (sec.)	a Duration Average (sec.)	a-E Interval Range (sec.)	a-E Interval Average (sec.)	RFW Ratio Range (%)	RFW Ratio Average (%)
Normal patient (64)	C	2-19	10 ± 3.6	0.03-0.13	0.06	0.03-0.28	0.10	30-84	57
	I	2-33	12	0.03-0.12	0.06	0.03-0.13	0.09	35-85	59
	2	2-23	12	0.03-0.13	0.06	0.03-0.18	0.10	20-100	63
	4	2-40	12	0.02-0.14	0.06	0.04-0.16	0.10	40-89	62
	10	2-4	12	0.03-0.13	0.06	0.03-0.17	0.09	39-92	59
Patient with ASHD (45)	C	8-48	22 ± 8.1	0.04-0.26	0.09	0.04-0.27	0.13	32-86	57
	I	8-146	34	0.04-0.24	0.09	0.04-0.24	0.14	19-121	69
	2	8-77	29	0.04-0.24	0.09	0.04-0.26	0.14	25-97	61
	4	9-77	29	0.04-0.24	0.09	0.05-0.26	0.14	35-88	59
	10	6-46	21	0.04-0.16	0.08	0.04-0.32	0.13	29-76	54

In the time column, C = control tracing, and I, 2, 4, and 10 represent immediately and at 2, 4, and 10 minutes after exercise. The numbers to the right of the ± sign represent the standard deviation.

Fig. 2. Group I. Normal ACG and ECG at rest and after exercise. Note absence of any change in the duration and amplitude of the a wave. The a-E interval remained unchanged.

mm. per second with 0.04-second time lines. The detailed technique for recording the ACG and its normal components has been described in previous works.

The "a" wave (ventricular filling due to atrial contraction), the RFW (rapid filling wave due to passive early diastolic filling of the ventricle), and the a-E interval (time from the peak of the "a" wave to the peak of the systolic wave) of the ACG were analyzed in all subjects at rest and after exercise. The "a" wave and RFW each were expressed as a percentage amplitude of the total tracing, i.e., "a" wave ratio $= \frac{a}{E\text{-}O} \times 100$, where "a" is the amplitude of the "a" wave in millimeters of deflection from its base line to its peak. E-O is the total amplitude of the tracing in millimeters of deflection from the E point to the O point.

Apexcardiograms were considered to be abnormal when the "a" ratio was above 20 per cent at rest or after exercise.

All measurements and ratios represent

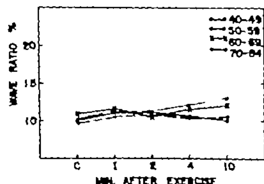


Fig. 3. Average "a" wave ratio of the ACG at rest and after exercise in various decades in 64 normal subjects. Note absence of any significant changes in the older decades.

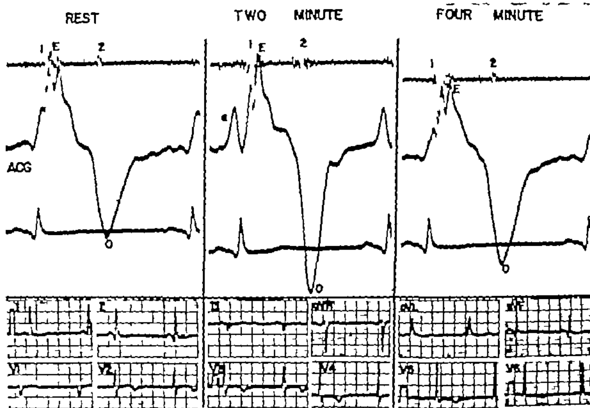


Fig. 4. ASHD Group IID. Note that the wave in the resting ACG is fused with the systolic wave. The resting ECG shows myocardial ischemia, left ventricular hypertrophy and signs of an inferior myocardial infarction. The ACG after exercise is abnormal with large wave and prolonged a E interval in the 2 minute tracing. The wave is again fused with the systolic wave in the 4-minute tracing. Observe that these changes in the E interval were completely independent of the length of the P R interval in the ECG.

the mean value of measurements made in three consecutive cardiac cycles.

Technical difficulties and limitations of the method. (1) Tracings were difficult and sometimes impossible to record in obese patients, especially in women with large pendulous breasts, in heavy-muscled men and in cases of pulmonary emphysema, left pleural effusion, mediastinal diseases and other conditions resulting in anatomic displacement of the heart. (2) This method is inapplicable in patients with atrial fibrillation or flutter since in this present study our criteria for positive diagnosis in the ACG are based mainly on abnormalities of the "a" wave. (3) Difficulties due to fast respiratory rate and tachycardia were found in some patients in recording the ACG at 1 minute after exercise. However, good recordings were obtainable at 2 minutes after exercise. (4) Accurate measurements of the "a" wave ratio cannot be obtained in patients with fast heart rate or with first-degree A-V block because of the superimposition of the a wave on the RFW.

Technique of recording the ACG. The position of the center of the apex beat is determined by palpation (patient in *left lateral decubitus position*) and the pickup device is placed exactly over the center of the apex and held *firmly* by hand or with a rubber strap. Tracings are always recorded at the end of *naturally held expiration* or in the beginning of *held inspiration*. The ACG has a reproducible wave form from beat to beat when these requirements are satisfied. Movement of the pickup device around the apex beat will cause interference in the base line and *artifactual* curves.

Results

Group I. Rest. As demonstrated in Fig. 1 all individuals had a wave ratios below 20 per cent. There were no significant dif

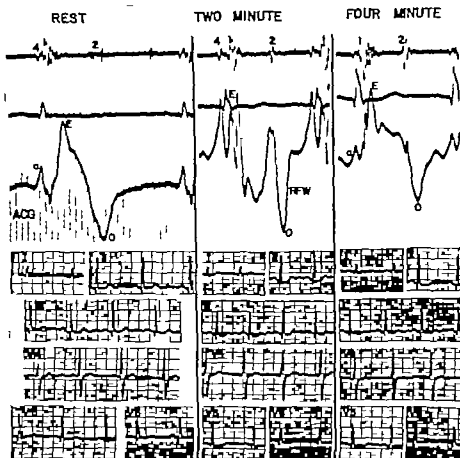
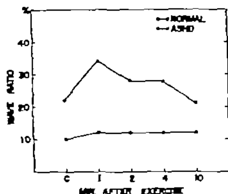


Fig. 5 ASHD Group IID (no MI and no AP). Abnormal ACG at rest and after exercise. Note the large 2 minute postexercise a wave. The ECG at rest shows flattening of the T waves. After exercise there was further depression of the T waves and of the S-T segment in Leads V V, and V



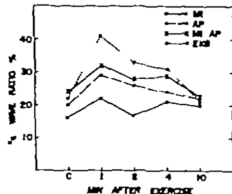


Fig. 6. Effect of exercise on the average wave ratio of the apexcardiogram in 64 normal subjects and in 45 patients with ASHD. Note the significant increase in this ratio immediately (*1*) and 2 minutes after exercise in patients with ASHD. See text.

Fig. 7 Average ratio at rest and after exercise in patients with myocardial infarction (MI—3 cases Group IIA), angina pectoris (AP—9 cases Group IIB), myocardial infarction and angina pectoris (MI and AP—16 cases, Group IIC), and in patients with abnormal electrocardiograms (ECG—17 cases, Group IID). Note greater increase of this ratio in Groups IIC and IID. See text.

ferences of those measurements in different age groups.

The duration of the "a" wave its percentage ratio a F interval and RFW ratios are illustrated in Table I

Four asymptomatic subjects (6 2 per cent) had borderline electrocardiograms at rest Two had flat T waves in several leads and 2 had complete right bundle branch block The exercise ECG in 4 showed equivocal changes, i.e depression of the J point of less than 4 mm. and flattening of the T waves. The ACG at rest and after exercise was normal in all 4 cases.

The other 60 electrocardiograms at rest were considered to be normal at rest.

Group I Exercise The exercise ECG was considered to be normal in 22 and borderline in 4 The ACG at rest and after exercise was normal in 60 subjects including those 4 with a borderline exercise ECG (Figs. 2 and 3) In the other 4 cases the ACG was borderline. All subjects had normal heart size on the chest x ray film and normal cardiovascular systems clinically

Group II Rest The duration of the "a" wave its percentage ratio the a E interval and RFW ratio are illustrated in Table I There was significant increase in the "a" wave ratio above 20 per cent in 55 6 per cent of the patients (25 patients) The other 44 4 per cent (20 patients) had normal ratios at rest (Fig 4) There was an increase in the duration of the "a" wave and the a E interval was prolonged (Table I)

Group II Exercise Of 45 patients, 44 4 per cent (20 patients) had normal "a" wave ratios at rest The ratio became abnormal upon exercise in 18 of these 20 (Fig 4) It continued normal in the other 2 patients.

Where the "a" wave ratio was abnormal at rest (25 patients) exercise produced greater alteration of previous findings in all cases (Figs. 5 and 6)

When resting and exercise were combined in this series of 45 patients, the ACG method was *positive* in 95.5 per cent (43 patients) with ASHD (Fig 6)

When the ASHD patients were studied separately the following results were obtained

Group IIA 3 patients with MI and no AP All patients had a normal "a" wave ratio at rest it became slightly abnormal upon exercise (Fig 7) All electrocardiograms at rest showed signs of MI The heart size on the x ray film was normal There was no evidence of heart failure.

Group IIB 9 patients with AP and no MI Six patients had a normal "a" wave ratio at rest it became abnormal in all after exercise (Fig 7) The other 3 patients had abnormal ratios at rest with greater alteration after exercise.

The ECG at rest was normal in 1 and abnormal in 8 patients with signs of myocardial ischemia Three patients without past history of coronary occlusion had signs of an old MI on the ECG

Four out of 9 patients had exercise electrocardiograms. The response to exercise was unchanged in 1 was greatly altered in 1 and was slightly changed in 2.

The heart size on x ray examination was normal in 8 patients and slightly enlarged in 1 patient. There were no clinical signs of heart failure in the 9 patients.

Group IIC 16 patients with MI and AP These patients represent the more severe cases of coronary disease on the basis of the past history of one or more episodes of acute MI and persistent AP

Two patients had a normal "a" wave ratio at rest and in 1 of these this became abnormal after exercise The other 14 patients had abnormal ratios at rest with greater alteration upon exercise (Figs. 6 7)

The patient with a normal ACG at rest and after exercise had frequent episodes of AP past MI abnormal ECG large heart size on x ray examination and was in mild heart failure

Fifteen of the 16 patients had electrocardiographic evidence of an old MI in *addition to the presence of myocardial* ischemia The other patient with a history of MI and AP had a normal ECG and ACG at rest but the exercise ACG was abnormal

The heart size on x-ray examination was normal in 12 patients and enlarged in 4 These 4 patients had slight dyspnea on effort, but denied the presence of orthopnea and paroxysmal nocturnal dyspnea The pulse rate was normal There was no hepatomegaly or peripheral edema.

Group IID 17 patients with abnormal ECG characteristic of ischemia no MI or AP The a wave ratio was normal at rest in 9 patients, and in 8 of these it became abnormal upon exercise (Fig 7) In the other 8 patients this ratio was abnormal at rest, with significant increase after exercise In these 17 patients the electrocardiograms at rest were normal in 2 patients, had signs of MI in 4 myocardial ischemia in 9 complete right bundle branch block in 1 and was borderline

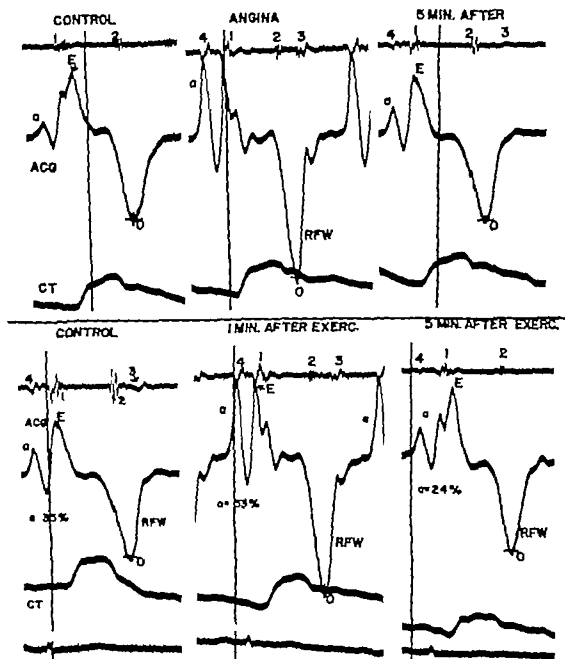


Fig 8 ASHD Group IIC (MI and AP). *Top* The tracings were recorded when the patient was experiencing spontaneous angina pectoris. Note very large "a and RFW coincident with fourth and third heart sound respectively during angina pectoris. *Bottom* Same patient as in the top tracings. These above changes were induced by exercise which also produced angina pectoris. CT Carotid tracing

in 1. The 2 patients with normal electrocardiograms at rest had borderline ECG response to exercise. The borderline resting ECG remained unchanged after exercise. The other 15 patients had definitely abnormal ECG response to exercise according to the previously described criteria.[6]

The single patient in this series of 17 who had a normal ACG at rest and after exercise had myocardial ischemia in the resting ECG.

Three patients showed slight enlargement of the heart on x-ray study, and 1 had clinical signs of heart failure.

Three patients in the entire series of 45 developed spontaneous AP while the ACG was being recorded. The "a" wave became very prominent during the anginal attack. These same changes were reproduced on the following day by exercise in all cases, also producing AP (Fig. 8). None of these patients were receiving digitalis which might have been responsible for the changes in the ECG after exercise.

Discussion

The previously described incidence of abnormality in the ballistocardiogram with aging[4] was not seen in the ACG of older patients with apparently normal cardiovascular systems.

In relation to the cause of the abnormal "a" wave in the ACG which occurred in 95.5 per cent of the patients with ASHD, the following facts have been documented. (1) We found an elevation of the pulmonary "wedge" pressure as have others,[8] as well as an elevation of the left atrial pressure. (2) The left ventricular end-diastolic pressure was elevated with a large "a" wave in the left ventricular pressure curve[4] (Fig. 9). (3) Cardiac output was normal at rest, with an increase after exercise (Table II).

With these findings, it is perhaps reasonable to postulate that an ischemic left ventricular wall has an increased resistance to distensibility; the end-diastolic pressure rises at the left ventricle, thus requiring a more vigorous left atrial contraction.

An alternative explanation for our findings is that an ischemic left ventricle would result in an incomplete systolic emptying with increased residual volume and therefore the ventricular end-diastolic pressure will rise in order to maintain an adequate cardiac output. In that case, if the other factors were equal, the ventricular diastolic pressure would be elevated even if the distensibility did not change. This, too, would result in an increased resistance to atrial contraction with a large "a" wave in the ACG.

Since these patients had normal cardiac output at rest,[10] with significant increase after exercise, it is therefore emphasized that on a strictly *hemodynamic basis* these hearts were *not* in typical *failure*. It should also be noted that this increase in cardiac output after exercise in 4 patients was made possible by an increase in the stroke volume as well as by an increase in heart rate (Table II). A typical failing heart usually increases the cardiac output during and after exercise at the expense of an increase in the pulse rate. The stroke volume remains unchanged or even decreases during and after the straining period of exercise. In addition, 40 patients with ASHD selected for this study had *no clinical* manifestation of *left ventricular failure* (recognized by the usual signs of dyspnea on effort, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, hepatomegaly, fast pulse rate, and cardiomegaly). Therefore, whether these hearts were compensated depends on the definition of heart failure.

Whether the "a" wave ratio could be used as an index of severity of ASHD and of response to therapy is an important question. In this regard, patients with a severe clinical picture of the disease (Group IIC) (Fig. 7), as judged by the number of episodes of AP and past histories of MI, had higher ratios than did those who had sustained a past MI and recovered without AP (Group IIA). The presence of a normal "a" wave ratio in patients with a previous myocardial infarction, who are *now* recovered and without angina, may prove to be a useful prognostic and therapeutic clue.

Of interest is the fact that 17 patients (Group IID) in the older age groups (asymptomatic, normotensive, and without valvular disease), without AP or MI but with electrocardiograms showing myocardial ischemia, had abnormal ACG at rest and after exercise.

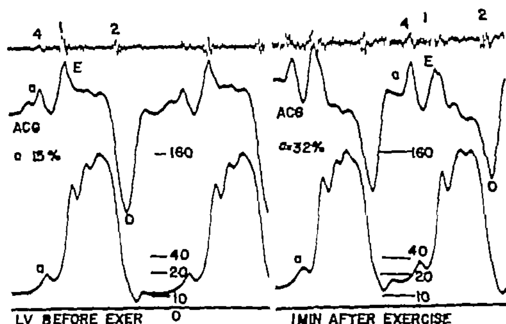


Fig 9 ASHD Group IIA (MI and no AP). The tracings were recorded during left heart catheterization. *Before Exercise.* A conspicuous w ve in the ACG large wave in the left ventricular pressure curves (LV), and elevation of the left ventricular end-diastolic pressure (20 mm. Hg). *After Exercise:* A further elevation of the left ventricular end-diastolic pressure with increase in the amplitude of the wa e of the ACG. Compare with Fig 10.

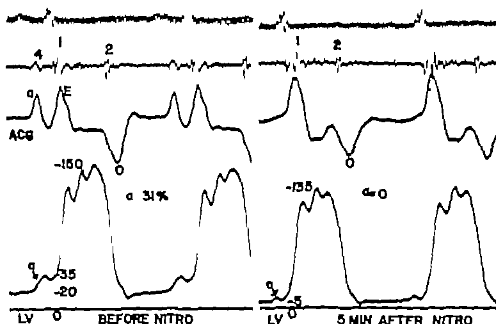


Fig 10 ASHD Group IIA (MI nd no AP). Same patient as Fig 9 The tracings ere recorded during left heart catheterization nd 10 min tes after exercise (see Fig 9). Note large wav (31 per cent) in the ACG large in he left ventricular pressure curve (LV), and an elev tion of the left ventricular end-diastolic pressure (35 mm. Hg). Fiv minutes after nitroglycerin (dre) there was complete disappearance of the w ve in the ACG ith significant decrease in the left ventricular end-diastolic pressure (7 mm. Hg).

Table II Cardiac hemodynamics at rest and during 7 minutes of exercise in 7 patients with ASHD (see text)

Patient	Group	Sex, age	B.S.A. (M^2)	Time	P.R. (min.)	C.O. (L./min.)	C.I. (L./min./M^2)	S.V. (c.c./beat)	S.I. (c.c./beat/M^2)	C.B.V. (L.)	C.B.V.I. (L./M^2)
1. W.U.	IIC	60, M	1.88	R	60	4.46	2.37	74	39	2.3	1.2
				F	84	9.60	5.10	114	60	3.9	2.1
2. C.R.	IIC	52, M	1.98	R	68	4.95	2.50	73	37	2.7	1.3
				E	72	7.20	3.64	100	50	3.1	1.6
3. J.R.	IIC	40, M	1.92	R	74	4.70	2.45	63	33	2.2	1.1
				E	116	8.58	4.46	74	38	3.0	1.5
4. B.M.S.	IIA	59, M	1.86	R	60	4.00	2.14	66	35	2.4	1.3
				E	100	6.41	3.44	64	34	3.8	2.0
5. T.F.	IIC	61, M	2.14	R	86	5.47	2.55	63	29	3.1	0.9
				F	120	6.11	2.85	51	23	3.2	1.5
6. L.C.	IIC	56, F	1.71	R	60	4.47	2.61	74	43	1.9	1.1
				F	112	9.31	5.44	83	48	2.8	1.6
7. H.W.	IIA	72, M	1.70	R	60	3.48	2.02	58	34	1.3	0.7
				Ex	96	4.92	2.89	51	30	1.9	1.1
Average increase					34	2.94	1.59	14	7	0.8	0.5

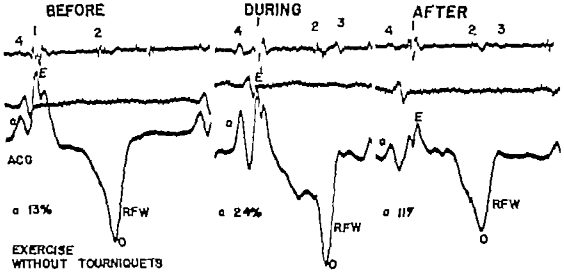
Cardiac output and index are within normal limits in all patients at rest. Note, however, that Cases 4 and 5 had an abnormal response to exercise, since the increase in the cardiac output was made possible by an increase in the heart rate with a decrease in the stroke volume. Cases 1, 2, 3, and 6 had a normal response to exercise since the stroke volume increased during exercise. All patients had an abnormal ACG at rest and after exercise.

CO: Cardiac output. CI: Cardiac index. SV: Stroke volume. SI: Stroke index. CBV: Central blood volume. CBVI: Central blood volume index. PR: Pulse rate. BSA: Body surface area.

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Apexcardiographic abnormalities in patients with ASHD are *not specific* since severe systemic arterial hypertension and aortic valvular lesions with no coronary *disease show changes which are in no way* different from those obtained in patients with ASHD This must also be applied to the changes seen in the electrocardiograms, also nonspecific for coronary disease. However the practical application of this method lies in the fact that, in cases in which clinical studies may suggest coronary disease an abnormal ACG may be present at rest or brought to light by moderate exercise. Others using different methods[13-15] have come to similar conclusions.

We are *now* studying the effect of nitroglycerin venous tourniquets cigarette *smoking* and hypotensive agents on the ACG in patients with ASHD Thus far we have found that nitroglycerin (Fig 10) venous tourniquets and the Kerr Lagen abdominal binder[1] (Fig 11) produce a beneficial effect on the ACG characterized by disappearance or diminution of the large a waves. Cigarette smoking reproduces the changes induced by exercise (Fig 12) When smoking or exercise is preceded by nitroglycerin or the applica



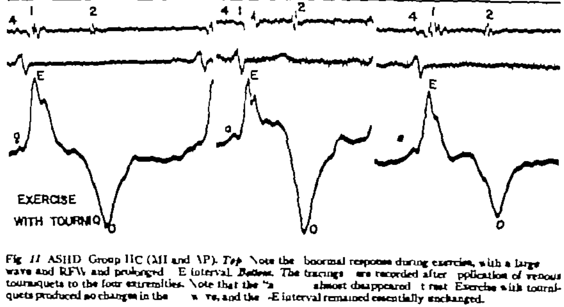


Fig 11 ASHD Group IIC (MI and AP). *Top* Note the abnormal response during exercise, with a large wave and RFW and prolonged E interval. *Bottom.* The tracings are recorded after application of venous tourniquets to the four extremities. Note that the "a almost disappeared at rest. Exercise with tourniquets produced no changes in the wave, and the -E interval remained essentially unchanged.

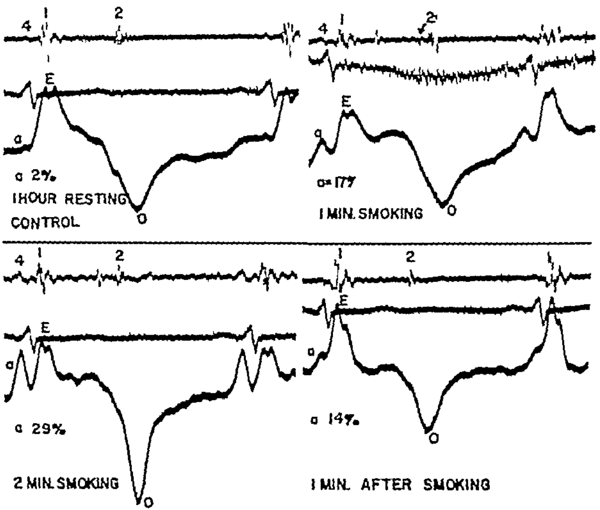


Fig. 1. ASHD Group IIC (MI and AP). Normal pexcardiogram at rest in patient with ASHD. Note a progressive increase in the amplitude and duration of the wave a t 1 minute and t 2 minutes after smoking. The P-R interval in the electrocardiogram remained essentially unchanged. The tracing returned to the control level 1 min t after smoking.

tion of tourniquets, these abnormal findings are prevented (Figs. 11 and 17).

We suggest that apexcardiography is a simple and practical test that provides objective evidence of heart damage in patients with ASHD and that normal older subjects without a clinical picture of ASHD do not present alteration in the ACG. Because of its ease, reliability, and reproducibility, this method lends itself to the study of the pharmacologic effect of drugs and other maneuvers in patients with ASHD. The fact that ischemic heart disease is associated with a rise in end-diastolic left ventricular pressure and left atrial pressure and that these wave forms can be recorded at the chest wall offers an open field for investigation not only of diagnostic maneuvers in angina, but of altered basic physiology.

Summary and conclusion

1. The ACG was studied at rest and after exercise in 64 subjects with normal cardiovascular systems who ranged in age from 40 to 84 years (average 54.6 years). It was demonstrated that aging per se did not produce abnormalities of the "a" wave in the ACG either at rest or after exercise.

2. In 55.5 per cent of the patients with ASHD there was significant abnormality at rest in the ACG, characterized by a large "a" wave and prolonged a-E interval. Exercise resulted in increased alteration of the above-mentioned findings. In 20

patients with ASHD and with normal tracings at rest, these alterations were provoked by exercise in 18

3 In 2 ASHD patients studied by cardiac catheterization catheterization of the right side of the heart in one showed significant elevation of the pulmonary wedge pressure and catheterization of the left side of the heart only in the other showed increased left ventricular end-diastolic pressure. There was further increase in these pressures after exercise with a marked increase in the a wave of the ACG The determination of cardiac output in 7 patients revealed normal cardiac dynamics at rest and after exercise in 4 of them in all 7 an abnormal a wave appeared upon exercise.

4. Patients with AP with or without MI and with electrocardiographic changes of ischemia had more significant abnormalities in the ACG than did those who had experienced coronary occlusion and recovered from it without AP

5 We suggest that the ACG provides a simple, practical useful and indirect way to objectively measure abnormalities present in patients with ASHD

We wish to thank Dr Jean F Legler Dr Y B Li, Dr Mark W Roberts, Dr Fernando R Carvalho, Miss Ellen Wright, and Mrs. Alexine Carvalho for their technical assistance.

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Differential hemodynamic effects of isoproterenol on mitral stenosis and left ventricular diseases

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Isoproterenol is a synthetic catechol amine with potent cardiovascula properties The drug causes a marked in crease in heart rate and in contractile force in the isolated and in the intact hearts of mammals. In very small doses it causes an increased myocardial oxygen consumption in perfused canine heart Isoproterenol is capable of increasing an idioventricular rate in the presence of complete atrioventricular block and in larger doses it may induce ectopic ar rhythmias In normal human subjects isoproterenol increases stroke volume heart rate and cardiac output and reduces peripheral vascular resistance Simultane ously the wedge pulmonary capillary or left atrial pressures are reduced There is evidence that isoproterenol causes peripheral venous constriction with a consequent increase in the pulmonary venous reservoir and central blood vol ume [7 8]

The hemodynamic response to the in fusion of isoproterenol in some respects resembles that to exercise isoproterenol thus serves as a useful agent for inducing acute hemodynamic alterations in patients undergoing studies in the physiology labo ratory

This investigation was undertaken to determine whether the hemodynamic re sponse to the infusion of isoproterenol that occurs in patients with tight mitral stenosis is sufficiently characteristic to permit differentiation of this group from patients who display an elevated resting pulmonary arterial or left atrial pressure due to mitral regurgitation or other left ventricular diseases. A second purpose of this paper is a further definition of two hemodynamically different groups of pa tients with tight mitral stenosis the strik ing hemodynamic differences between these two groups of patients with tight mitral stenosis are accentuated by the infusion of isoproterenol

Methods

A Patients From approximately 80 cardiac patients who had been studied hemodynamically during the intravenous infusion of isoproterenol 37 were selected for review Excluded were those patients

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who had lesions predominantly of the right side of the heart, those in whom the control or experimental data were inadequate, those who had complex multivalvular lesions, and those in whom the predominant lesion was not clearly established by hemodynamic or angiographic studies or by surgery.

The 37 patients were divided into four groups according to the following criteria: *Group 1* (n = 9) having tight mitral stenosis (calculated mitral valve orifice area less than 1.2 cm.²) proved at surgery, and having only a moderately reduced resting cardiac output (greater than 2.0 L./min./M.²). *Group 2* (n = 5) having tight mitral stenosis (calculated mitral valve orifice area less than 1.2 cm.²) proved at surgery in 3, and having a marked reduction of resting cardiac output (less than 2.0 L./min./M²). *Group 3* (n = 12) having pure or obviously predominant mitral regurgitation demonstrated hemodynamically and proved at the time of mitral annuloplasty in 7 patients. *Group 4* (n = 11) having left ventricular diseases other than mitral valve disease, but inclusive of aortic stenosis (3), aortic regurgitation (1), coarctation of the aorta (1), systemic hypertension (4), and arteriosclerotic heart disease (2). Four of these patients displayed hemodynamic evidence of left ventricular failure.

Table I shows the data in regard to age, sex, cardiac rhythm, and proof of diagnosis for each of the 4 groups. Of particular interest are the predominance of females in those groups with mitral valve disease, and the infrequent occurrence of atrial fibrillation in Group 4.

B. Procedure. After the usual clinical, radiologic, and electrocardiographic evaluation, catheterization of the right side of the heart was performed with the patient unsedated and in the fasting state. Local anesthesia was used at the site of the venous cut-down and arterial puncture. The catheter was passed to the main pulmonary artery; a Cournand needle was placed in a radial or brachial artery. Pressures were measured by means of a Statham P23D pressure transducer and were recorded using a Sanborn amplifier and photographic recorder. The zero pressure base line was corrected to a reference level 10 cm. above the table with the patient supine. Mean pressures were obtained by electronic integration.

Ventilation and oxygen consumption were measured by means of a 13.5-liter Collins respirometer using 100 per cent oxygen. When a steady state of oxygen consumption was obtained, records of pressure and samples of blood were obtained from the pulmonary artery and systemic artery. The venous catheter was then advanced to the wedge pulmonary capillary position and a pressure record was obtained. Cardiac output was determined by the direct Fick principle

Table I. Case material

	Group				Totals
	1 *MS*	*2* *MS* *(low CI)*	*3* *MR*	*4* *Other left heart disease*	
Number	9	5	12	11	37
Surgical proof	9	4	7	2	22
Males/Females	0/9	1/4	2/10	8/3	11/26
Mean age	42	46	40	43	
NSR	6	1	3	10	20
AF	3	4	9	1	17

MS: Mitral stenosis. MR: Mitral regurgitation. CI: Cardiac index. NSR: Normal sinus rhythm. AF: Atrial fibrillation.

in all but a few patients in Group 4 in whom the dye-dilution technique was utilized

An intravenous infusion of isoproterenol in 5 per cent dextrose in water (0 4 microgram per milliliter) was then administered at a rate of 60 to 120 drops per minute 0 0_ to 0 04 microgram per kilogram per minute The drip rate was adjusted to a level at which acceleration of the heart rate occurred This increase exceeded 10 beats per minute in all patients except 2 ne patient displayed an increase of 7 beats per minute and the other an un explained decrease of 10 beats per minute. The total duration of infusion of isoproterenol usually ranged between 15 and 30 minutes. When a new steady state of oxygen consumption occurred repeat records of pulmonary arterial and systemic terial pressure and samples of blood were btained as was also a record of wedge pulmonary capillary pressure

Some patients described a sensation of facial flushing precordial pounding or of nervousness during the infusion of isoproterenol and premature ventricular contractions occurred in some patients. When the latter developed the drip rate of isoproterenol was reduced until the premature ventricular contractions disappeared No adverse reactions to the drug were observed under these conditions. During the entire procedure the electrocardiogram and pulmonary arterial or wedge pulmonary capillary pressures were monitored

C Data and statistical method Each patient served as his own control Direct measurements of minute ventilation minute oxygen consumption arteriovenous oxygen difference mean systemic pulmonary and wedge pulmonary capillary pressures and heart rate were obtained From these were derived the cardiac output, stroke output mitral valve diastolic flow per diastolic second mitral valve orifice area[16] (Formula 1*) and apparent right ventricular minute (Formula 2†) and stroke work. The total pulmonary pulmonary vascular and systemic resistances were calculated (Formula 3‡)

In order to permit comparison of groups of patients values of flow resistance and work are corrected to the body surface area.

The data were processed in a 09 digital computer which was programmed to derive the means standard deviations, and cross correlations. The p values of significance of the differences between the control and the isoproterenol means were calculated by the *t* test

Results

Table II lists for each patient the measured and derived hemodynamic parameters obtained during the control period and during the infusion of isoproterenol The mean control and experimental values for each group together with statistical evaluations are recorded in Table III

The infusion of isoproterenol resulted in similar responses in all groups. The minute ventilation was increased although not significantly the arteriovenous oxygen difference was narrowed the heart rate was significantly increased in all groups, as was also cardiac output. Although stroke index tended to increase slightly in Group 4 none of the groups showed a significant change in this variable. Therefore the increased cardiac output was due primarily to marked acceleration of heart rate rather than to an increase in stroke volume.

There was little change in mean blood pressure during the infusion of isoproterenol. Systemic resistance fell significantly in all but Group 1 in which the decrease was not significant.

Because the cardiac output increased and because the diastolic filling period was shortened with increased heart rate, the

*(1) Mitral valve orifice area (cm.^{2}) = $\dfrac{\text{Mitral valve flow (ml./diastolic second)}}{31 \sqrt{PC_{mean} - 5}}$

†(2) Apparent right ventricular minute work index (Kg.M./min./M.^{2}) = $\dfrac{\text{(Cardiac index) (.063) (13.6) (Pulmonary arterial mean)}}{1\ 000}$

‡(3) Resistance indices dynes sec. cm.$^{-5}$ × M.^{2} = $\dfrac{\text{(Mean pressure) (1 332) (60)}}{\text{Cardiac index}}$

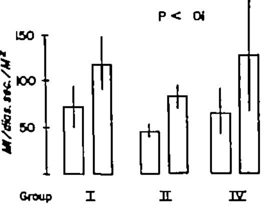


Fig. 1 Increases in mean mitral valve flow with infusion of isoproterenol for three of the four groups of patients (p <.01). Flows are expressed as milliliters per diastolic second per square meter of body surface. The unshaded bars represent the group mean mitral flow at rest, whereas the shaded bars represent the group mean mitral flow during infusion of isoproterenol. The standard deviation for each value is indicated by the vertical line. Mitral valve flows are not indicated for the patients of Group 3, since the regurgitant flow volumes were not measured.

rate of mitral diastolic blood flow per diastolic second was significantly increased in all groups, as may be seen in Fig 1 Values for Group 3 are not included in the figure nor in the tables since the regurgitant flow was not quantitated in these patients.

The control pulmonary arterial and pulmonary capillary pressures were elevated in all groups being greatest in Group 1 On the basis of the Gorlin formula[1] for mitral valve orifice area, it would be anticipated that isoproterenol induced increases in mitral valve flow per diastolic second of this magnitude should raise pulmonary arterial and pulmonary capillary or left atrial pressures in patients with tight mitral stenosis. In Fig 2 the response of pulmonary arterial and pulmonary capillary pressures to the infusion of isoproterenol for each patient is recorded. All patients in Group 1 showed a significant increase of 20 per cent or greater in mean pulmonary capillary pressure and a slightly lesser increase in pulmonary arterial pressure during the infusion of isoproterenol. Patients in Group 2 who had tight mitral stenosis but a low resting cardiac output demonstrated a lesser and nonsignificant increase in mean pulmonary arterial and pulmonary capillary pressures. Two patients in Group 2 showed no increase in pulmonary capillary pressure during the infusion of isoproterenol in spite of a significantly increased mitral valve flow none of the patients of Group 2 showed a fall in pulmonary pressures, however Patients in Group 3 all of whom had dominant mitral regurgitation demonstrated variable responses of the pulmonary pressure. Three of the patients in this group who displayed increases of more than 20 per cent in pulmonary pressures during the infusion of isoproterenol had minimal mitral stenosis in addition to predominant mitral

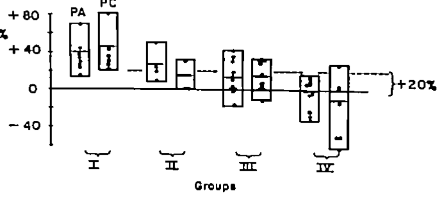


Fig. 2 The percentage changes in mean pulmonary arterial pressures (*PA*) and wedge pulmonary capillary pressures (*PC*) induced by infusion of isoproterenol in four groups of patients. Individual mean pressure changes are indicated by dots. The mean pressure change for each group is indicated by horizontal line.

Table II Values at rest and during infusion of isoproterenol for individual patients in each group

Patient		Ventilation (L./min./M.²)	O consumption (ml./min./M.²)	A-V O₂ difference (ml./L.)	Heart rate (beats/min.)	Cardiac index (L./min./M.²)	Stroke index (ml./beat/M.²)	PA mean pressure (mm. Hg)
Group 1 (= 9)								
E.S.	C	5 8	137	64	89	2 2	24	25
	I	6 4	159	65	173	2 4	14	32
W W	C	6 0	151	56	89	2 7	30	54
	I	6 2	171	52	112	3 3	29	88
M C.	C	4 9	119	55	44	2 1	49	30
	I	—	172	35	85	3 4	40	51
L C.	C	5 7	138	63	60	2 2	37	22
	I	5 3	182	39	94	4 7	51	28
E.R.	C	6 0	144	62	91	2 3	26	26
	I	5 5	157	45	124	3 5	28	32
E G	C	—	160	39	88	4 1	47	39
	I	—	190	39	110	5 0	45	44
R J	C	4 0	155	48	83	3 1	37	16
	I	4 5	149	47	107	3 0	28	22
H C	C	6 1	163	70	98	2 4	25	48
	I	6 7	198	54	152	3 8	24	68
R P	C	4 3	119	57	66	2 1	32	31
	I	4 0	130	44	78	3 0	28	39
Group 2 (= 5)								
L.B	C	5 0	145	77	64	1 9	29	24
	I	8 6	150	65	79	2 3	29	26
J.G.	C	3 5	104	0	68	1 5	22	12
	I	4 7	139	58	78	2 4	31	14
M W	C	3 8	118	73	102	1 6	16	26
	I	5 0	154	51	144	3 1	21	39
M Z.	C	4 9	122	80	96	1 5	16	12
	I	5 3	135	56	144	2 4	17	16
M.S.	C	4 3	177	69	51	2 0	39	20
	I	15 8	199	56	114	3 6	31	24
Group 3 (= 12)								
A.Q	C	4 8	155	67	65	2 3	35	28
	I	7 5	173	50	80	3.5	45	28
F O.	C	6 5	137	68	72	2 0	28	25
	I	6 2	158	66	133	2 4	18	34
M.E.	C	4 6	165	60	80	2 7	34	24
	I	4 6	162	44	96	3 7	41	25
J W	C	—	148	66	62	2 3	36	40
	I	—	160	56	92	2 9	31	—
J D	C	8 3	133	60	72	2 2	31	26
	I	8 0	122	53	85	2 3	27	29
A.P	C	4 5	133	60	100	2 2	22	18
	I	7 0	151	51	140	3 0	21	18

Atrial fibrillation. C: Control value at rest. I: Value during infusion of isoproterenol. PA: Pulmonary artery. PC: Pulmonary "capillary" pages 808-809.

PC mean pressure (mm. Hg)	Arterial mean (mm. Hg)	Mitral valve flow (ml./diastolic sec./M^2)	RV minute work (Kg.M./min./M^2)	RV stroke work (Kg.M./beat/M^2)	TPR index (d.s.c.$^{-5}$ × M^2)	PVR index (d.s.c.$^{-5}$ × M^2)	Systemic resistance (d.s.c.$^{-5}$ × M^2)	Body surface area (M^2)
16	88	88	0 65	007	910	328	3 200	1 30
28	81	81	0 97	006	1 100	168	2 690	
—	75	84	1 91	022	1 600	—	2 220	1 54
—	64	122	3 96	036	2 667	—	1 550	
22	86	50	0 76	017	1 140	301	3 270	1 44
40	—	105	2 62	038	1 260	260	——	
19	100	59	0 54	005	800	110	2 910	1 71
24	90	139	1 56	017	475	66	1 530	
22	76	67	0 70	008	904	136	2 650	1 53
31	76	118	——	——	——	——	1 740	
30	80	116	2 02	023	762	177	1 560	1.54
39	62	174	2 82	026	705	81	995	
15	——	98	0 49	006	414	26	——	1 68
18	78	117	0 74	007	566	108	2 040	
21	100	62	1 49	015	1 600	898	3 330	1 53
32	120	138	3 47	023	1 430	755	2 520	
26	125	61	0 79	012	1 182	193	5 150	1 66
35	137	94	1 48	019	1 140	106	3 650	
19	106	57	0 39	006	1 010	210	4 470	1 75
21	102	71	0 53	007	905	174	3 310	
10	93	38	0 15	003	641	107	4 980	1 62
—	88	67	0 31	004	462	—	2 930	
22	96	43	0 39	004	1 300	205	4 810	1 64
29	83	98	0 98	007	1 050	302	2 140	
11	60	45	0 13	001	640	55	3 200	1.58
11	66	80	0 21	001	535	131	2 210	
12	82	46	0 59	011	800	330	5 370	2 09
12	90	99	1 10	010	535	269	2 200	
20	102	—	0 95	014	970	288	3 539	1 57
26	109	—	1 45	018	612	46	2 498	
19	72	—	0 74	010	1 005	230	2 790	1 74
25	74	—	1 20	009	1 130	300	2 460	
19	85	—	0 95	012	700	146	2 481	1 56
20	—	—	1 36	014	540	104	——	
25	90	—	—	—	—	—	—	——
25	—	—	—	—	—	—	—	
17	66	—	0 84	012	942	328	2 410	1 48
20	—	—	0 94	011	1 010	315	—	
15	90	—	0 58	006	655	190	3 284	1 56
15	90	—	0 79	005	450	80	2 410	

...ary RV: Right ventricular. TPR: Total pulmonary resistance. PVR: Pulmonary vascular resistance. Table II is continued on

Table II—Cont'd

Patient		*Ventilation* (L./min./M.²)	*O₂ consumption* (ml./min./M.²)	*A-V O₂ difference* (ml./L.)	*Heart rate* (beats/min.)	*Cardiac index* (L./min./M.²)	*Stroke index* (ml./beat/M.²)	*PA mean pressure* (mm. Hg)
Group 3 (n = 12)—Cont'd								
M.G.	C	3.6	119	57	82	2.1	26	20
	I	4.5	142	56	102	2.5	[illegible]	[illegible]
D.D.	C	5.2	134	56	100	2.4	24	22
	I	6.1	153	48	90	3.2	35	18
A.S.	C	2.6	133	52	48	2.6	53	16
	I	5.6	170	38	84	4.5	54	18
L.G.	C	3.3	125	65	67	1.9	29	24
	I	6.6	138	43	110	3.2	29	34
A.S.	C	4.3	150	44	84	3.5	42	11
	I	4.5	168	56	108	3.0	28	13
A.B.	C	3.0	128	43	60	3.0	50	10
	I	3.4	167	36	8	4.6	53	10
Group 4 (n = 11)								
S.G.	C	5.4	163	61	67	2.7	40	22
	I	6.2	1 4	22	109	8.0	73	21
C.B.	C	3.6	146	42	81	3.4	42	24
	I	4.2	200	36	92	5.5	59	17
L.M.	C	4.1	106	45	75	2.4	32	40
	I	4.5	157	50	82	3.1	3	44
H.G.	C	—	—	—	92	2.4	26	26
	I	—	—	—	108	2.8‡	26	30
M.W.†	C	—	100	—	88	0.8	10	59
	I	—	129	—	101	1.1‡	11	69
R.B.†	C	—	180	100	94	1.7	18	54
	I	—	177	78	101	2.8‡	28	52
O.R.†	C	—	144	—	88	1.3	14	55
	I	—	147	—	108	2.2‡	20	59
P.H.	C	5.4	162	38	92	3.7	40	32
	I	7.6	161	35	113	4.6‡	41	20
E.R.	C	3.4	131	68	90	2.5	27	56
	I	9.8	143	55	114	3.6‡	32	60
A.L.	C	4.4	137	36	64	3.7	59	12
	I	4.8	173	30	88	5.7	65	8
E.H.	C	4.1	143	51	33	2.8	33	17
	I	5.2	187	32	2	5.8	81	15

*Atrial fibrillation.
†Left ventricular failure.
‡Cardiac output determined by dye-dilution technique.
Abbreviations are as given in the footnote on pages 806-807.

regurgitation at the time of operation. The patients of Group 4 who had various left ventricular diseases showed a mean decrease in pulmonary pressures during the infusion of isoproterenol. Only one of the entire group showed an increase in pulmonary capillary pressure of more than 20 per cent from the resting level.

From these data the following conclusions may be drawn: (1) An increase in

Valsalva s maneuver in atrial septal defect

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The effect of the Valsalva maneuver or prolonged forced expiration with an open glottis on arterial blood pressure and heart rate and the abnormal response in heart failure were first described in detail with modern methods by Hamilton and associates. Many authors have since described clinical applications of the square wave or heart failure response.[-4] Fig 1 illustrates the normal response. The deep inspiration which precedes the strain produces a slight fall in arterial pressure. There is a brief rise in pressure with the beginning of the strain as blood is forced out of the thorax.[3] As the strain continues there is a marked fall in systolic pressure and pulse pressure as the obstructed venous return leads to a fall in stroke output heart rate increases during this period. When the strain is released there is a brief fall in pressure as intrathoracic blood volume is reconstituted. After this the surge of venous return causes an increased stroke output and there is a hypertensive overshoot particularly of systolic pressure[4] the systolic overshoot is accompanied by transient reflex bradycardia.

In the square wave or heart failure response (Fig 2) the strain produces simply a passive rise equally of systolic and diastolic pressures and no change in heart rate. After release there is a simple return to the control pressure with no systolic overshoot or bradycardia. Presumably the stroke output is little altered through the whole maneuver in these cases. Many patients have responses which are intermediate between the typical normal and the typical square wave response illustrated.

Abnormal responses have been noted in mitral stenosis,[4] pulmonary vascular disease kyphoscoliosis various *forms of con*genital heart disease[4] and constrictive pericarditis, in addition to heart failure. Lee and Gimlette reported square wave responses in 2 patients with atrial septal defect and heart failure suggesting that the abnormal response explained the lack of transient shunt reversal in these patients after the strain transient shunt reversal being demonstrable by ear oximetry in other patients with atrial septal defect. This was confirmed by McIlroy who also found negative oximetry tests in 21 of 71 patients with atrial septal defect without heart failure and attributed this to square wave Valsalva responses in uncomplicated atrial septal defect with greatly increased pulmonary blood flow.

In examining this further we noticed intermediate abnormal responses in the great majority of patients with atrial septal defect and wondered whether this might be a useful diagnostic test for the

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PC mean pressure (mm. Hg)	Arterial mean (mm Hg)	Mitral valve flow (ml./diastolic sec./M²)	*RV* minute work (Kg M./min./M²)	*RV* stroke work (Kg M./beat/M²)	*TPR* index (d.s.c⁻⁵ × M²)	*PVR* index (d.s.c⁻⁵ × M²)	Systemic resistance (d.s.c⁻⁵ × M²)	Body surface area (M²)
18	64	—	0 62	005	766	77	2 450	1 65
24	84	—	0 96	009	819	63	2 520	
20	—	—	0 78	008	730	—	—	1 46
—	—	—	0 85	009	410	—	—	
9	97	—	0 61	013	492	215	2 980	1 97
8	78	—	1 19	014	319	177	1 385	
18	80	—	0 67	010	965	235	3 340	1 55
24	80	—	1 60	015	845	235	1 995	
9	91	—	0 58	007	249	45	2 056	1 88
9	90	—	0 57	005	333	93	2 400	
—	100	—	0 44	007	266	—	2 660	1 58
—	95	—	0 68	008	174	—	1 650	
12	96	75	0 83	013	659	315	2 876	1 90
6	80	236	2 47	022	212	156	807	
16	105	98	1 21	015	563	187	2 460	1 80
8	—	165	1 35	015	246	133	—	
32	93	64	1 41	019	1 342	154	3 100	1 72
41	77	152	2 00	024	1 160	77	2 040	
16	136	64	0 92	010	865	320	4 550	1 58
—	116	76	1 24	011	858	—	3 310	
45	—	25	0 69	008	5 900	1 400	—	1 77
39	98	35	1 12	011	5 030	3 190	7 130	
38	120	46	1 36	014	2 340	760	5 650	1 80
39	106	96	2 14	021	1 480	370	3 030	
36	96	34	1 05	012	3 390	1 170	5 910	1 71
36	104	63	1 92	018	2 140	840	3 780	
23	200	96	1 74	019	690	194	4 340	1 47
	200	127	1 06	009	348	—	3 490	
32	148	63	2 06	023	1 790	770	4 740	1 86
—	156	99	3 18	028	1 330	—	3 480	
8	96	103	0 65	010	259	86	2 070	2 10
3	96	210	0 67	008	112	70	1 345	
13	129	65	0 70	015	486	114	3 710	1 84
8	136	157	1 26	018	207	87	1 850	

pulmonary arterial pressure and either pulmonary capillary or left atrial pressure of greater than 20 per cent during infusion of isoproterenol is compatible with but not diagnostic of tight mitral stenosis (2) A fall in pulmonary arterial and pulmonary capillary pressure during infusion of isoproterenol suggests left ventricular disease and is evidence against significant mitral stenosis. (3) A failure

Table III Mean values for each group of patients at rest and during infusion of isoproterenol

	Ventilation (L./m ./M)	O con mp-tion (ml./min./M)	A V O_2 d fferenc (ml./L.)	Heart rate (beats/min.)	Cardiac index (L./m n./M)	Stroke index (ml./beat/M)	PA mea pressure (mm. Hg)
G oup 1 (= 9)							
	7	9	9	9	9	9	9
C	5 4	143	57 1	78 7	2 58	34 1	32 3
(SD)	(8)	(15 4)	(8 7)	(16 8)	(62)	(8 7)	(11 7)
I	5 5	168	46 7	115	3 57	33 0	45 0
(SD)	(93)	(20 4)	(8 7)	(29 1)	(78)	(10 8)	(19 9)
Δm	0 1	25	10 4	36 3	99	1 1	12 7
Δm	+2	+17	−18	+46	+39	−3	+40
p	NS	< 01	< 05	< 01	< 01	NS	NS
G oup 2 (= 5)							
	3	5	5	4	5	5	5
C	4 3	133	73 8	76 2	1 70	24 4	18 8
(SD)	(59)	(25 6)	(4 2)	(19 5)	(21)	(8 7)	(5 9)
I	7 9	155	57	112	2 76	25 8	23 8
(SD)	(4 3)	(22 9)	(4 5)	(29 3)	(51)	(5 7)	(8 9)
Δm	3 6	22	16 6	35 6	1 06	1 4	5 0
Δm	+84	+17	−23	+46	+63	+6	+27
p	NS	NS	< 001	< 05	< 001	NS	NS
G p 3 (= 1)							
	11	12	12	12	12	12	11
C	4 61	138	58 2	74 3	2 43	34 2	20 4
(SD)	(1 56)	(12 9)	(8)	(13)	(44)	(9 4)	(5 7)
I	5 82	155	49 8	100 6	3 23	33 9	23 0
(SD)	(1 3)	(14 5)	(8 2)	(18 5)	(71)	(11 4)	(7 8)
Δm	1 21	17 0	8 4	26 3	80	3	2 6
Δm	+26	+13	−15	+36	+33	−1	+13
p	NS	< 01	< 05	< 001	< 01	NS	NS
Group 4 (= 11)							
	7	10	8	11	11	11	11
C	4 34	141	33 1	80 4	2 49	32 8	36 1
(SD)	(74)	(23 5)	(19 9)	(13 1)	(89)	(14 9)	(16 6)
I	6 04	165	42 2	98 9	4 11	43 0	35 9
(SD)	(1 8)	(20 5)	(16 8)	(13 1)	(1 91)	(23)	(20 5)
Δm	1	13 8	12 9	18 5	1 62	10 2	2
Δm	+39	+10	− 4	+22	+63	+31	− 5
p	< 05	NS	NS	< 01	< 05	NS	NS

Number of pat ents C Cont l value at rest. I Value during infusion of isoproterenol (SD) Standard deviation. Δm Difference mentary ca illary RV Righ vent icular TPR Total pulmonary resistance, PVR Pulmonary vascular resistance

PC mean pressure (mm Hg)	Arterial mean (mm. Hg)	Mitral valve flow (ml./diastolic sec./M²)	RV minute work (Kg M/min./M²)	RV stroke work (Kg M/beat/M²)	TPR index (d.s.c.⁻⁵ × M²)	PVR index (d.s.c.⁻⁵ × M²)	Systemic resistance (d.s.c.⁻⁵ × M²)
8	7	9	8	8	8	7	7
21 4	93 4	71 7	1 08	013	1 051	290	3 003
(4 6)	(19 5)	(21 5)	(58)	(006)	(387)	(266)	(1 041)
30 9	90 0	119 4	2 20	022	1 150	221	2 097
(6 9)	(26 3)	(28 3)	(1 11)	(011)	(649)	(227)	(837)
9 5	3 4	47 7	1 12	009	99	69	1 005
+45	−4	+67	+103	+65	+9	−24	−33
< 01	NS	< 001	< 02	< 01	NS	NS	NS
4	5	5	5	5	5	4	5
16 0	87 4	45 8	33	005	878	131	4 146
(4 6)	(15 7)	(6 2)	(17)	(003)	(251)	(76)	(762)
18 3	85 8	83 0	63	006	698	185	2 598
(7 3)	(11 7)	(13 3)	(36)	(003)	(233)	(70)	(541)
2 3	1 6	37 2	30	001	180	53	1 548
+15	−2	+81	+90	+20	−21	+41	−38
NS	NS	< 01	NS	NS	NS	NS	< 001
10	8	—	11	11	11	9	8
16 9	87 0	—	705	010	704	195	2 837
(4 6)	(12 9)	—	(154)	(003)	(259)	(87)	(466)
19 6	87 0	—	1 06	011	609	157	2 276
(6 4)	(10 7)	—	(32)	(004	(293)	(97)	(304)
2 7	0	—	35	001	95	37	611
+16	0	—	+50	+10	−14	−19	−21
NS	NS	—	< 01	NS	NS	NS	< 01
8	9	11	11	11	11	8	9
25 0	123 7	66 6	1 15	014	1 660	523	4 105
(13 3)	(33 2)	(24 3)	(44)	(004)	(1 623)	(487)	(1 207)
22 5	119	128 3	1 68	017	1 193	615	2 570
(16 4)	(37 2)	(59)	(71)	(006)	(1 366)	(1 003)	(1 017)
2 5	4 7	61 7	53	003	487	92	1 535
−10	−4	+93	+46	+18	−29	+18	−37
NS	NS	< 01	< 05	NS	NS	NS	< 01

between means. %Δm $\frac{\Delta m}{Cm}$ 00 p: Probability of significance. NS Not significant (p .05). PA, Pulmonary artery PC: Pul-

of pressures to rise more than 20 per cent during infusion of isoproterenol does not exclude tight mitral stenosis, since such a response may be seen in patients with tight stenosis and a very low resting cardiac output.

Apparent work per minute of the right ventricle was increased in both groups of patients with mitral stenosis. Since stroke volume was not significantly increased by isoproterenol in either group, the increased minute work was entirely due to increased rise in pulmonary arterial pressure and to increased heart rate. Apparent right ventricular stroke work was increased by 65 per cent in Group 1, whereas it increased by only 20 per cent in Group 2 during infusion of isoproterenol.

This failure of right ventricular stroke work to increase significantly during the infusion of isoproterenol in the patients of Group 2 who had a low resting cardiac output comprises a further point of hemodynamic differentiation from the patients of Group 1. In neither group of patients with mitral stenosis was stroke volume significantly increased by isoproterenol; thus increases in stroke work must reflect primarily increases in pulmonary pressure. Since the mitral valve flow per diastolic second achieved during the infusion of isoproterenol in Group 1 was 66 per cent higher than the resting level, this could be achieved only by a major increase in mitral valve gradient, i.e., a major rise in pulmonary and left atrial pressure. Right ventricular systolic contractile force and right ventricular stroke work were therefore increased.

Conversely, the resting mitral valve flow per diastolic second and the resting stroke volume were at very low levels in Group 2. Therefore, resting pulmonary pressures also were relatively low. With isoproterenol stimulation, the mitral valve flow per diastolic second was increased by 81 per cent, but the absolute level of this higher mitral valve flow per diastolic second was only slightly greater than that of the patients of Group 1 at rest. Such an increase in mitral valve flow, although relatively marked, was still low enough that a major increase in mitral valve gradient was not required to attain this flow; pulmonary pressures therefore did not rise significantly, and right ventricular stroke work was not appreciably increased.

The initially lower cardiac index and stroke volume seen in the patients of Group 2 cannot be attributed to pulmonary vascular disease, inasmuch as the pulmonary vascular resistance was not increased in these patients. There was no hemodynamic evidence of right ventricular failure, since all patients of Group 2 had normal right ventricular end-diastolic pressures. It is unlikely that hypovolemia was responsible for the low resting cardiac output and stroke volume in the patients of Group 2, since estimates of "effective blood volume" obtained with Evans blue dye demonstrated normal values for each of 3 patients in the two groups.

Thus the low resting stroke volume and relatively low mitral valve flow per diastolic second explain the relatively low resting pulmonary arterial pressures and right ventricular stroke work in the patients of Group 2. The failure of pulmonary pressures and of stroke work to increase significantly with the infusion of isoproterenol is due to the failure of mitral valve flow to reach levels requisite of a marked increase in mitral valve pressure gradient. These patients appear to have adapted to obstruction of the mitral valve orifice by a marked reduction in stroke volume, rather than by an increase in right ventricular systolic contractile force such as is seen in the patients of Group 1.

Discussion

The differentiation of the various causes of an elevated left atrial pressure is of great practical importance. In a patient with noncritical mitral stenosis an elevated left atrial pressure may be due to left ventricular failure, which, if not recognized, may lead to a faulty conclusion that the mitral stenosis is critical and operable. Ideally, a transmitral valve pressure gradient should be measured whenever left atrial pressures are elevated. The infusion of isoproterenol provides an additional simple method of distinguishing the elevated left atrial pressure due to mitral stenosis from that occurring with mitral regurgitation or other left ventricular diseases. An increase in pulmonary capil-

lary and pulmonary arterial pressures of more than 20 per cent from the resting level during infusion of isoproterenol is compatible with critical mitral stenosis but is not diagnostic of obstruction of the mitral valve since, occasionally a patient with mitral regurgitation or left ventricular diseases showed a similar response. Conversely a fall in these pressures during the infusion of isoproterenol is strong evidence against critical mitral stenosis and favors predominant mitral regurgitation or some other left ventricular disease as a cause of elevated resting pulmonary pressures. Similar results have been reported (as abstracts) from this and other laboratories.[11,12] It is important to note that patients with tight mitral stenosis, who have a markedly reduced resting cardiac output and normal or only mildly elevated resting pulmonary pressures may not display a significant increase in pulmonary pressures during infusion of isoproterenol (Group 2)

The fact that tight mitral stenosis may on occasion display misleadingly low pulmonary and left atrial pressures when the resting cardiac output is markedly reduced further emphasizes the necessity of measurements of flow as well as of pressure.

There are two major hemodynamic adaptations available to severe obstruction of the mitral valve. The majority of patients maintain an adequate resting cardiac output by increasing the pressure gradient across the mitral valve i.e. the left atrial pressure is increased The minority of patients with a similar degree of restriction of the mitral valve adapt by a marked reduction in stroke volume and cardiac output, thus avoiding an otherwise obligatory high pressure gradient across the mitral valve

The elevated resting pulmonary arterial and left atrial pressures displayed by the majority of patients with tight mitral stenosis are attained by a forceful right ventricular systolic ejection since stroke volume and cardiac output are normal or only mildly reduced increased right ventricular stroke and minute work reflect the elevated pulmonary arterial pressure The stimulus to increased systolic contractile force of the right ventricle is not clearly defined but may in part involve the greater resistance to systolic ejection imposed upon the right ventricle by the stenosed mitral valve. The infusion of isoproterenol causes an increase in cardiac output by increasing heart rate with a consequent increase in mitral valve flow per diastolic second. In accordance with the Gorlin orifice formula such an increase in flow requires a mandatory increase in mitral valve pressure gradient. Left atrial pulmonary capillary and pulmonary arterial pressures must therefore also increase. This necessitates a further increase in right ventricular systolic ejection force and right ventricular stroke work.

The adaptation to obstruction of the mitral valve by a marked reduction in stroke volume is displayed by the patients of Group 2 of this series. This response although infrequently encountered has been described by a number of investigators.[13,14] Since the volume of blood presented at the stenotic mitral valve is small a minor pressure gradient will suffice to attain this flow Left atrial, pulmonary capillary and pulmonary arterial pressures need not be much elevated. Since stroke volume is reduced and pulmonary pressure is near normal the right ventricular systolic work is subnormal With isoproterenol stimulation it would be anticipated that the inotropic effect of the drug would result in an increase in right ventricular systolic contractile force and stroke work Although minute cardiac output is increased this is due entirely to an increased heart rate since stroke volume is unchanged. Nevertheless mitral valve flow per diastolic second is significantly increased because of the shortened diastolic filling period. Since mitral valve flow per diastolic second even with isoproterenol stimulation is still subnormal (approximately that of the patients of Group 1 at rest) the mitral valve pressure gradient need not be great. Left atrial and pulmonary pressures are thus increased only slightly as are right ventricular systolic ejection force and stroke work. Although a further substantial increase in cardiac output and stroke volume would of necessity involve significant increases in left atrial pressure and right ventr

of pressures to rise more than 20 per cent during infusion of isoproterenol does not exclude tight mitral stenosis since such a response may be seen in patients with tight stenosis and a very low resting cardiac output.

Apparent work per minute of the right ventricle was increased in both groups of patients with mitral stenosis. Since stroke volume was not significantly increased by isoproterenol in either group, the increased minute work was entirely due to increased mean pulmonary arterial pressure and to increased heart rate. Apparent right ventricular stroke work was increased by 65 per cent in Group 1, whereas it increased by only 20 per cent in Group 2 during infusion of isoproterenol.

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Case report

Pulmonary ossific nodule formation in the absence of mitral valve disease

A report of four cases

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In recent years, several papers concerning the presence of ossific nodules in cases of mitral valve disease have appeared in the literature.[1-8] The presence of these nodules has always been regarded as a rare association of mitral disease, and most reports have been of isolated or small groups of cases. During a recent survey of 200 cases of mitral valve disease, Galloway and associates found ossific nodules radiologically in 13 per cent of the cases. A pathologic survey showed that in mitral valve lesions, and particularly in mitral stenosis, ossific nodules could be found by histologic examination at autopsy in over 50 per cent of the cases.

Pulmonary venous hypertension was the most significant clinical finding, as shown by symptomatology, radiology, and catheter studies. Lendrum and associates[10] first suggested that ossific nodules were formed by metaplasia in areas of pulmonary intra-alveolar edema, and this hypothesis appeared to fit in with the data obtained from the group of cases of mitral valve disease with ossific nodules. On theoretical grounds, if this hypothesis is correct, nodules should develop in other disorders in which there is long-standing pulmonary venous hypertension. We are now reporting 4 cases without evidence of mitral valve disease. Since in all 4 cases there were ossific nodules on histologic examination of the lungs, they are described in some detail in view of the light they throw on the etiology of this condition.

These cases were seen during the pathologic survey undertaken by Galloway and associates,[9] when evidence was being sought of the presence of ossific nodules in association with conditions other than mitral valve disease, and particularly in cases in which pulmonary arterial or venous hypertension had been present.

In addition to the 4 cases to be described in more detail, the lungs from 12 other patients were examined. These patients included 4 with aortic stenosis, 2 of whom had been in left ventricular failure, 1 with aortic incompetence, 2 with essential hypertension, 1 with left ventricular failure, 1 with constrictive pericarditis and pulmonary congestion, 2 with chronic bronchitis and cor pulmonale

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and 1 with congestive cardiac failure and an atrial septal defect.

All these patients were examined during a period of 6 months, in a busy 850-bed general hospital with a special cardiological service and were quite unselected. The same procedure was followed with all patients on whom an autopsy was performed during this time, and in whom there was a long history of cardiac disease.

The lungs were examined by a method previously described by Galloway and associates.[1] This briefly is as follows: "The lung is divided into separate lobes which are then cut into slices of approximately one centimetre thickness in the coronal plane. A contact radiograph is taken of each lung slice and carefully examined for the presence of ossific nodules. Suspicious areas are then examined histologically after preliminary decalcification. In addition, blocks are taken at random mainly from the lower lobes and studied in serial section for the presence of ossific nodules.

Case reports

Case 1. Patient A.R.

HISTORY. This 37-year-old woman was first hospitalized on Feb. 22, 1960, with a 2-month history of rapidly progressive effort breathlessness, orthopnea, and upper abdominal pain aggravated by exertion. One year previously she had had an episode of severe constricting pain across the chest, radiating to both arms, which had lasted for 1 or 2 minutes and had then completely cleared. A similar episode occurred 6 months later. Three weeks before admission to the hospital, she had had weakness of the left arm and leg which lasted for 5 minutes, and which was followed by complete recovery. There was no rheumatic history and nothing of note in the family history. Her three pregnancies had all been normal.

On examination she was ill, cyanosed, and had slight distention of the neck veins. The heart was enlarged, with a tapping apical impulse; the pulse was regular and of small volume, and the blood pressure was 100/75 mm. Hg. A triple rhythm was audible at the apex, but no murmurs could be heard. Rhonchi were audible over both lung fields, and the liver was enlarged 4 inches below the costal margin. There was no ascites and no edema.

The electrocardiogram showed sinus rhythm with broad dome-shaped P waves and the pattern of right ventricular hypertrophy. The chest films showed definite enlargement of the right ventricle and right atrium and slight left atrial enlargement. The anterior pulmonary artery segment was prominent, and septal lines were visible in both lung fields (Fig. 1). The hemoglobin was 11.2 Gm. per 100 ml. of blood, the white blood cell count was 8,600 per cubic millimeter with a normal differential count, and the erythrocyte sedimentation rate (Westergren) was 24 mm. in 1 hour.

She was treated with bed rest, digitalization, salt restriction, and oral diuretics, and her general condition improved. During the next few days splinter hemorrhages were noted under the fingernails, and a retinal hemorrhage appeared; there was no pyrexia and the spleen was not palpable. Urine microscopy showed the presence of a few red blood cells. Blood cultures were made but subsequently no growth was obtained. Treatment with penicillin and streptomycin was started because of a presumptive diagnosis of subacute bacterial endocarditis, and was continued for 6 weeks. At this time a mitral presystolic murmur was first heard.

Her condition gradually improved, although there was a persistent tachycardia and frequent bouts of profuse sweating without pyrexia. She was allowed to return home after 2 months in the hospital, free of heart failure but considerably restricted in effort tolerance.

Two months later she was rehospitalized in congestive cardiac failure, and again she improved on treatment. On this occasion soft apical systolic and diastolic murmurs were intermittently audible.

On Aug. 1, 1960, she was hospitalized for the third time, again in congestive cardiac failure. A pulmonary infarct developed at the base of the right lung 3 weeks after admission, and this was associated with a rapid deterioration in her condition with intense cyanosis and peripheral circulatory collapse. She died on Aug. 22, 1960.

AUTOPSY FINDINGS. The heart weighed 473 grams and both ventricles were dilated. Two centimeters below the pulmonary valve the thickness of the right ventricular wall was 4 mm. and the average thickness of the left ventricular wall was 18 mm. A large lobulated tumor which measured 6.3 by 5.0 by 3.5 cm. almost completely filled a dilated and hypertrophied left atrium and was attached to the margin of the annulus ovalis by a short pedicle. The tumor completely occluded the mitral orifice and had been grooved by the mitral ring where it protruded into the left ventricle. The mitral valve ring was dilated but had normal valve cusps and was without evidence of bacterial endocarditis.

The tumor showed the microscopic appearances typical of an atrial myxoma. A firm antemortem thrombus occluded a main branch of the pulmonary artery which supplied the right lower lobe and had produced infarction of a major portion of the lobe. There was an ulcerated atheromatous plaque deep to the thrombus. The left lung was retained for pulmonary arteriography. There was no evidence of venous thrombosis in the calf or pelvic veins.

Histologic examination of blocks taken from the right lung showed a patchy distribution of mild to moderate intimal and medial hyperplasia of the small muscular pulmonary arteries. There was also intimal hyperplasia of the arterioles. The alveolar septa showed capillary dilatation with increase of fibrous tissue and there were areas which contained eosinophilic intra-alveolar exudate. Hemosiderin-laden macrophages were seen in some of the alveoli, principally in subpleural areas.

Contact radiography of 1-cm. slices of the right



Fig 1 Case 1 (A.R.). Posteroanterior chest film which show left ventricular enlargement and pulmonary interstitial edema with a few basal septal lines, which do not show well on the reproduction.

l ng was also carried out, and several radiopaque areas pinhead in size were seen mainly in the lower lobe Most of these areas examined histologically after preliminary decalcification were shown to consist of lamellar bone

The final diagnosis therefore w that of a left atrial myxoma with terminal pulmonary artery thrombosis. The appearance of the mall pulmonary vessels suggested that mild pulmonary arterial hypertension had been present.

Case 2 Patient W H

HISTORY This 50-year-old man was first seen in July 1954 with 6-month history of angina on effort associated with breathlessness Ther was nothing of note in the previous history both parents nd two siblings had heart d sorders. Bouts of paroxysmal nocturnal dyspnea had developed in the few weeks before he was admitted t the hospital, where he wa found to ha left ventricular enlargement, apical gallop rhythm a blood pressure of 210/130 mm Hg and crepitations t both lung bases.

An electrocardiogram showed the hanges of a old posterior infarction and recent terior myocardial infarction. The chest film showed hilar looding lamellar effusions and left ventricular enlargement. After he was treated with digoxin, diuretics and salt estriction his condition improved lthough his hypertension and gallop rhythm persisted.

I September 1955 he w rehospitalized in congestiv cardia failure still with blood pressure of 220 130 mm. H After the heart failure was controlled, treatment w th pentolinium w commenced. This lowered his blood pressure but wa followed by further myocardial infarction which w treated with anticoagulants. After critical illness he eventually recovered and was allowed to return home. He was well enough in February 1957 to take up a part-time clerical job. At that time his failure was controlled with diuretics and his blood pressure was 160/110 mm. Hg without hypotensive drugs In December 1957 September 1959 and April 1961 he had further episodes of myocardial infarction, and during this time his blood pressure fell to level of 130/100 mm. Hg nd his gallop rhythm persisted. On April 17 1961 he was hospitalized with combined left and right heart failure after a prolonged bout of severe chest pain. The electrocardiogram was difficult to interpret, but the serum transaminase levels were raised and because he was thought to have had a further myocardial infarction he was treated with anticoagulants and a cardiac-failure regimen. The chest film was interpreted as showing severe pulmonary venous hypertension with cute pulmonary alveolar edema (Fig 2). Initially there was some response t treatment, but he died suddenly 1 month after admission.

AUTOPSY FINDINGS. The tracheal and bronchial mucosa were markedly hyperemic, and the lumina contained mucopurulent material. There were bilateral fibrinous pleural adhesions, and both lungs felt firm and were edematous and congested. The pulmonary artery and its main branches showed marked atheroma but no thrombosis or embolic occlusion could be demonstrated.

The heart weighed 750 grams, and both entricles were grossly dilated and hypertrophied The verage thickness of the left ventricular wall was 20 mm., and that of the right ventricular wall was 9 mm. There was dilatation of both the tricuspid and



Fig 2 Case 2 (W H). Posteroanterior chest film which show generalized cardiac enlargement that affects mainly the left ventricle There is lso marked pulmonary interstitial edema.

condition. We here present quantitative observations on the Valsalva response in 36 patients with atrial septal defect as compared with that in 50 normal subjects with an analysis of the value of this test in the detection of the presence of an atrial defect and in the assessment of the size of the left-to-right shunt, and with some observations on the factors which influence the response.

Case selection and methods

The 36 patients with atrial septal defect were 9 to 58 years of age and were a representative group referred to a university center for investigation and surgical treatment of this condition. With the few exceptions noted in Table I, they had secundum defects without complicating lesions other than partial anomalous pulmonary venous connections or left superior vena cava and were without serious pulmonary hypertension; the pulmonary arterial systolic pressures were less than 50 mm. Hg. Only one had ever had overt congestive heart failure. All had pulmonary systolic murmurs, widely split second sounds, and left-to-right shunts at the atrial level proved by cardiac catheterization. All had normal sinus rhythm. Direct proof of interatrial communication was obtained by operation or passage of the catheter into the left atrium in all but 3 patients.

The left-to-right shunt was calculated in each case from blood oxygen contents determined by the Van Slyke method. Pulmonary arteriovenous difference was obtained by subtracting pulmonary arterial oxygen content from a pulmonary venous content assumed to equal 95 per cent of capacity when arterial blood was equilibrated with room air. In those cases in which samples of pulmonary venous blood were obtained, there was good agreement with this assumption. Systemic arteriovenous difference was taken as the mean content of samples from the superior and inferior venae cavae subtracted from the same calculated pulmonary venous content. In the 11 cases in which only the superior vena caval sample was obtained, the inferior vena caval oxygen content was assumed to equal 0.9 vol. per cent higher than the superior vena caval oxygen content, this being the mean difference in the 24 cases in which both were measured. The shunt was not calculated in one case with incomplete data.

Twenty normal subjects were studied by arterial puncture, 12 males and 8 females who were 17 to 54 years of age. Three of these were healthy personnel of the laboratory, 5 were college students with slight labile systolic hypertension, 2 were patients with mild polycythemia vera, and 10 were patients with innocent murmurs; atrial septal defect was not seriously suspected in any of this last group, and catheterization of the right side of the heart in 7 gave normal results. An additional 30 normal subjects were studied without arterial puncture, the electrocardiogram being used to measure the heart rate response only. This group included 11 children, 8 to 14 years of age, who were patients in the hospital for various minor conditions not affecting the cardiovascular system, and 19 were healthy hospital personnel, 18 to 45 years of age.

The Valsalva maneuver was performed with the patient in the supine position by inspiring deeply and then blowing forcibly through a mouthpiece into an aneroid manometer, maintaining a pressure of 40 mm. Hg for 10 to 12 seconds. An 18-gauge needle introduced into the apparatus as a constant leak ensured near-equilibrium of intra-oral and intrabronchial pressure throughout the straining procedure. Direct arterial pressures were obtained from indwelling needles in the brachial artery. During cardiac catheterization, the right heart pressure was recorded simultaneously, providing further proof of the correct performance of the maneuver. The mean heart rate and systolic and diastolic pressures of 10 consecutive beats immediately before the strain were taken as the control values. Many measurements of the response were made and four were selected as the most useful: (1) the average pulse pressure of the 3 consecutive beats during the strain which showed the greatest reduction from the control pulse pressure, (2) the average heart rate of the 3 consecutive beats during the strain which showed the greatest increase over the control heart rate (a change hereafter referred to as the "strain tachycardia"), (3) the systolic pressure of the

mitral valve rings, probably with associated incompetence, although there was no organic valvular disease. The coronary arteries were grossly atheromatous, and there was recanalization of the anterior descending and circumflex branches of the left coronary artery. A recent thrombus occluded the right coronary artery 3 cm. distal to its origin. There was extensive fibrosis of the wall of the left ventricle, and a partly organized mural thrombus was present in the septal region.

A congested liver showed evidence of cardiac cirrhosis. The kidneys were also congested with some cortical atrophy and areas of scarring. Histologic examination of the lungs showed slight intimal and medial hypertrophy of the small muscular pulmonary arteries, together with patchy areas of arteriolar intimal hyperplasia. The alveolar septa were thickened with an increase in fibrous tissue and moderate capillary dilatation. Eosinophilic material lined many of the alveoli and simulated hyaline membrane. Some alveoli contained hemosiderin-laden macrophages.

Contact radiography of 1-cm. slices from both lungs was carried out. Numerous radiopaque areas, up to 3 mm. in diameter, were seen mainly but not exclusively in the lower lobes (Fig. 3). Histologic examination showed these areas to be composed of lamellar bone (Fig. 4, *A* and *B*). A few of the nodules could be shelled out from the lung. They were mulberry shaped and apparently had been molded by the lung lobules (Fig. 5).

The final diagnosis in this case was that of essential systemic hypertension, coronary artery atherosclerosis, with extensive myocardial fibrosis, and remote and recent myocardial infarctions. The histologic appearances of the small pulmonary vessels indicated mild or moderate pulmonary arterial hypertension consistent also with the right ventricular hypertrophy.

Case 3. Patient H. C.

HISTORY. This 59-year-old man gave a history of 6 months of general malaise associated with progressive effort breathlessness and swelling of the feet, but initially he was without orthopnea. His condition improved after 3 weeks of bed rest, but he suffered a relapse as soon as he increased his activities. In the 6 weeks before admission to the hospital he developed a nonproductive, irritating cough which was associated with orthopnea, abdominal swelling, and gross edema of the legs. He had not had any chest pain. There was nothing of note in the family history. He had previously had malaria, typhoid, and dysentery.

On examination he was of stocky build, icteric but not cyanosed. The jugular venous pressure was grossly elevated, and the exact level could not be determined, even with the patient sitting upright. The pulse was regular and of poor volume; the blood pressure was 120/100 mm. Hg. The cardiac impulse was not palpable; the heart sounds were distant, and a soft third sound was audible at the lower end of the sternum. Crepitations could be heard at the lung bases. The liver was markedly enlarged; there was ascites and gross edema of the sacrum, scrotum, and legs. A chest film showed a normal-sized heart with pulmonary congestive changes and indefinite septal lines. The electrocardiogram showed sinus rhythm,

Fig. 3. Case 2 (W.H.). Postmortem contact x-ray film of a 1-cm. slice of lung taken from the right lower lobe. Visible are several ossific nodules of varying size.

low voltage complexes, and flat T waves over the left ventricle.

Laboratory studies showed a hemoglobin of 15.2 Gm. per 100 ml. of blood, and a white blood cell count of 10,200 per cubic millimeter. The serum bilirubin was 4.3 mg. per cent, and the serum alkaline phosphatase was 29 King-Armstrong units. The serum proteins measured 7.0 Gm. per 100 ml. of blood, the albumin being 4.37 and the globulins 2.63 Gm., respectively, and the serum nonprotein nitrogen was 60 mg. per 100 ml. of blood.

Some improvement followed treatment with bed rest, digitalis, and diuretics. The jugular venous pressure fell to a level of 7 cm., and the edema cleared almost completely. His condition later deteriorated, and he died 3 weeks after admission in a confusional state with increasing congestive cardiac failure.

AUTOPSY FINDINGS. The pleurae were normal and the tracheal and bronchial mucosae were hyperemic. The lungs on section showed congestion of the upper lobes and congestion and edema of the lower lobes. The heart was small and weighed 275 grams. The visceral and parietal layers of the pericardium were markedly thickened and adherent. Small areas of the pericardium were calcified. The myocardium was firm on incision and showed subpericardial fatty infiltration. The coronary arteries were tortuous

F 44 Case 4 (W T). Low power ew of an nodule which shows lamellar bone and osteo-

Fig. 48. High-power ew of Fig 44 taken with polarized light to show the bone lamellae in greater detail (hematoxylin and eosin ×250).

had thickened walls, and showed moderate atheroma, but no occlusions or areas of stenosis could be seen. The liver showed cardiac cirrhosis. There was a well-defined primary renal carcinoma, 3.5 cm. in diameter at the upper pole of the left kidney

Histologic examination of the lungs showed several medium-sized muscular pulmonary arteries (1,500 to 2,500 microns in diameter) occluded by *organized thrombi*. In a few of the sections calcium had been deposited t the periphery of the thrombus just beneath the intima. *Occasional areas of bone* formation were seen in the deposits of calcium. The alveolar septa showed moderate capillary congestion and also scattered areas of fibrosis. Areas of intra al eolar eosinophilic exudate were seen on some of the sections. The small muscular pulmonary arteries showed no evidence of medial hypertrophy and there was only *minimal arteriolar intimal thickening* Slices of lung were examined by contact radiog raphy but no *radiopaque areas could be found*. Random blocks from the lower lobes were examined histologically after preliminary decalcification. Intra-alveolar bone nodules were found in two of the blocks. The bone was lamellar in type, and no intermediate tages of woven bone or osteoid tissue could be found.

The final diagnosis here was *one of constrictive* pericarditis the renal carcinoma was an incidental finding There was nothing to suggest more tha mild rise in pulmonary arterial pressure.

Case 4 Patient W T

HISTORY This 57 year-old man had first bee hospitalized with severe epistaxis 4 years previously when he was found to ha e a blood pressure of *200/100 mm. Hg* No underlying cause could be found for the hypertension and he was treated with *mecamylamine*, but with poor control. The blood pressure aried from 190/110 to 240/130 mm. Hg I the 7 months before admission to the hospital he had developed progressi effort breathlessness, orthopnea and later swelling of the nkles. He had n t had any chest pain. There had been no previous illnesses, and there was nothing of note in the family history

On examination he had Cheyne-Stokes breathin was confused but not cy nosed The blood pressure was *200/140 mm. Hg* and the pulse was regular with an pical gallop rhythm. Crepitation ere audible t the lung bases, together with evidence of congestiv ardiac failure. There w re Stage II hypertensi retinal hanges nd also albumi uria. The electrocardiogram showed left tricular hy pertrophy and there was moderat cardiac enlargement on the chest film, with hilar loadin and lamellar effusions.

H improved on treatment and although his nonprotein nitrogen w slightly raised t 46 mg per 100 ml. of blood, an intra enous py logram showed good excretion of the dy by both kidneys. Ther was recurrence of heart failure when he allowed to increase his act ities and his cond ional tat recurred. H became pyrexial with of consolidation t the base of the left lung d he died suddenly 1 week late w thout any hange in his condition.

AUTOPSY FI DINGS. The trachea and bronchi re filled with mucus, and few pleural adhesions ere

Fig 5 Case 2 (W.H.). Photographic enlargement of an ossific nodule 3 mm. in diameter taken from the lower lobe of the right lung

present at the base of the right lung. Both lungs were congested and edematous, and there was consolidation in the left lower lobe. The heart weighed 675 grams. Moderate left ventricular hypertrophy and dilatation were present. The average thickness of the left ventricular wall was 22 mm., and the right ventricular wall measured 5 mm. The heart valves were normal. A dissecting aneurysm of the aorta was present; this commenced just above the aortic valves and tracked along the whole of the aorta into the common iliac vessels. The coronary arteries were patent, minimal atheroma was present, and the myocardium was normal on section. The left kidney was recently infarcted, due to thrombotic occlusion of an atheromatous left renal artery. The right kidney was slightly congested but otherwise normal.

Histologic examination showed capillary congestion of the lungs, with slight hyperplasia of the intima of the arterioles and small muscular pulmonary arteries. There was no medial hypertrophy. Hemosiderin-laden macrophages were frequently seen in the alveoli. Contact radiography of lung slices did not reveal any macroscopic ossific nodules. Intra-alveolar nodules of lamellar bone were found on histologic examination of random blocks from the lower lobes.

The final diagnosis was one of essential hypertension with minimal coronary atherosclerosis, but with incidental renal artery thrombosis. The dissecting aneurysm of the aorta was the terminal event. The pulmonary arteries and arterioles showed evidence of only minimal pulmonary arterial hypertension.

Comment

All 4 patients were severely incapacitated by breathlessness and congestive cardiac failure.

Because of severe orthopnea they all required the use of a back rest and several pillows during their terminal illness. Two of them had recurrent bouts of paroxysmal dyspnea (Cases 1 and 2). Septal lines were visible on the chest film in Case 1. Cases 2 and 4 showed the presence of lamellar effusions and hilar congestive changes, and Case 3 had lamellar effusions alone. Septal lines are evidence of an existing or previously raised pulmonary venous pressure and are usually associated with a mean pulmonary capillary wedge pressure of 20 mm. Hg or above in mitral stenosis.[11,12] Similarly, lamellar effusions and hilar congestion may be taken as evidence of left heart failure[14] and, hence, of pulmonary venous hypertension. In left ventricular failure these two features are more commonly found than septal lines, which are often obscured by pleural transudates. Orthopnea and paroxysmal dyspnea are also evidence of pulmonary venous hypertension, since Dexter and associates,[16] Lewis and associates, and Selzer and McCaughey[17] have shown that patients with these symptoms due to *left ventricular failure usually have a* resting mean pulmonary wedge capillary pressure of 20 mm. Hg or above. Although cardiac catheterization studies were not made in any of these patients, it is reasonable to assume on clinical and radiologic grounds that they all had a high pulmonary venous pressure.

In all 4 patients the ossific nodules were intra-alveolar and were composed of mature lamellar bone (Fig 4). They did not differ from those found in mitral valve disease and macroscopically had a similar mulberry-shaped appearance (Fig 5). A careful search was made of serial sections of the bone nodules and also *of other areas* of lung tissue in an attempt to find various stages in the development of the nodules. Areas of hyaline intra-alveolar edema and *of organizing exudate were not infrequent,* particularly in the lower lobes, but neither the early stages of nodule formation nor nodules of immature woven bone could be demonstrated. The 2 patients with *ossific nodules* visible on contact radiography had the longest case histories—18 months (Case 1) and 7 years (Case 2). The nodules were more florid in Case 2 with the longer history. Hemosiderosis was

present histologically in the lungs of 3 patients, although it was never very marked and was not visible on the chest films.

Ossific nodules were not found in any of the other 12 cases studied in detail although 3 patients were in left ventricular failure and 2 others had symptomatic and radiologic evidence of pulmonary venous hypertension

Radiologically visible ossific nodules have never been described in disorders in which pulmonary arterial hypertension occurs in the absence of pulmonary venous hypertension as in chronic chest disorders, such as chronic bronchitis and emphysema in congenital heart disease and in primary pulmonary hypertension In addition to the 1 case of atrial septal defect and the 2 patients with cor pulmonale on whom detailed autopsy studies were undertaken without the finding of any histologic evidence of bone formation we have studied a large number of chest films from patients with various types of pulmonary arterial hypertension but we have never observed ossific nodules. Two patients with left ventricular failure of long standing due to coronary artery disease are at present under observation with 3-year and 5-year histories. The patient with the 5-year history has basal changes suggestive of early ossific nodule formation although the changes are much less marked than in mitral valve disease The clinical history of this patient is similar to that of Case 2 described in this paper

Discussion

Several hypotheses have been put forward to explain bone formation in the lungs of patients with mitral stenosis. Salinger[1] suggested that a combination of pulmonary congestion and pneumonia resulted in small areas of parenchymal fibrosis in which bone formed by metaplasia and Elkeles and Glynn[1] also thought that a rheumatic pneumonia was the main initiating factor Lawson[11] and Ellman and Gee[12] suggested that hemosiderosis was the precursor of ossific nodules, but Whittaker and associates[6] Fleming and Robinson[7] and Galloway and associates[9] all found inconspicuous hemosiderin in the lung sections from their patients with bone nodules.

Whittaker and associates,[6] in reviewing 7 cases of pulmonary ossific nodules considered pulmonary arterial hypertension of great importance in the pathogenesis, and Fleming and Robinson[7] reporting on 8 patients also thought that pulmonary arterial hypertension was an important factor and further noted that all their patients had evidence of pulmonary venous hypertension in that septal lines were visible on all the chest films.

Microscopic bone nodules have been described in the Hamman Rich syndrome (diffuse interstitial pulmonary fibrosis) by Beams and Harmos[14] and by Wildberger and Barclay[illegible] and they appear to develop in organizing intra-alveolar exudate. In both reports the patients were males and they had histories of 15 months and 7 years duration respectively

Subcutaneous ossification in the legs of patients with chronic venous insufficiency has been described by Lippmann and Goldin[16,17] They thought that the orthostatic edema due to the high venous pressure was an important factor in causing heterotopic bone formation There was a higher incidence of leg ulceration and chronic cellulitis in their patients with bone formation and the inflammatory reaction may have been of importance in its pathogenesis. A point of great interest was the development of heterotopic bone in tissue subjected to a high venous back pressure and this clearly bears comparison with the state of chronic pulmonary venous hypertension

Galloway and associates[9] reviewed 27 cases of ossific nodules in relation to mitral valve disease and found that pulmonary venous hypertension was the most significant common factor Lendrum and associates[18] first put forward the hypothesis that nodule formation took place in small areas of pulmonary intra-alveolar edema which had become organized by fibroblasts and converted into bone by a process of metaplasia This hypothesis fitted in well with most of the observed facts, which can be briefly stated as follows The bone nodules are intra alveolar they may develop in the absence of pulmonary arterial hypertension pulmonary arterial hypertension of the pre-capillary type is not associated with ossific nodules

long-standing pulmonary venous hypertension develops in mitral stenosis, which is the classic condition associated with ossific nodule formation.

Despite their absence radiologically bone nodules were demonstrated histologically at autopsy in over 50 per cent of the lungs examined from patients with mitral valve disease.[9] This suggested that it would be worth while to examine the *lungs in other disorders which produce* pulmonary venous hypertension The most common cause is left ventricular failure secondary to hypertension coronary artery disease or aortic valve disease. Other and much rarer disorders include left atrial myxoma or thrombus, cor triatriatum and pulmonary venous occlusion

Including the 4 patients whose cases have been described here a total of 16 cases has been examined at autopsy for ossific nodules. Eight patients had clinical and radiologic evidence of pulmonary venous hypertension and Table I shows the duration of pulmonary congestive symptoms. The first 4 patients are those described in detail here.

The rate of development of the nodules is difficult to assess, although we have seen them appear radiologically in a case of mitral valve disease 3 years after the onset of pulmonary congestive symptoms. Ossific nodules were seen on contact radiography in only the 2 patients with symptoms of at least 18 months duration (Table I) They were larger and more numerous in Case 2 (W.H.) with a 7 year history (Fig 3) The nodules formed in Cases 3 and 4 were small and few in number Although they were not found in the other 4 patients with symptoms of 5 to 12 months duration the findings suggest that the size and frequency of the bone nodules increase with prolongation of symptoms. It is possible that sparse minute areas of bone formation may be missed when random blocks of lung are examined and nodules are not seen on *contact radiography This method of assessment* is liable, therefore, to underestimate the frequency of bone formation

Organizing intra alveolar exudate was found on many of the lung sections, but none of the intermediate stages in the development of the nodules was observed. The nodules are intra alveolar are composed of lamellar bone and differ in no way from those in mitral valve disease. We have previously shown the presence of nodules of woven bone in cases of mitral stenosis, with osteoid tissue at the periphery and on some sections a mixture of woven and lamellar bone has been seen. The nodule formation appears, therefore, to follow the general lines of development of heterotopic bone described by Curran and Collins.[22,23] The intra-alveolar exudate becomes organized by proliferating mesenchymal cells which produce woven bone by a process of metaplasia. The woven bone is then later replaced *by the apposition* of mature lamellar bone. There was no evidence of calcification without bone formation, and the woven bone develops by calcification of osteoid tissue.

There was no clinical or autopsy evidence

Table I

Case		Diagnosis	Duration of congestive symptoms	Histologic ossific nodules	Ossific nodules on contact radiography
1	A.R.	Atrial myxoma	18 mo.	+	+
2	W.H.	Left ventricular failure, coronary artery disease, hypertension	7 y	+	+
3	H C	Constrictive pericarditis	6 mo.	+	–
4	W T	Left ventricular failure, hypertension	7 mo.	+	–
5	J.B	Left ventricular failure, aortic stenosis	8 mo.	–	–
6	J.R.	Left ventricular failure, aortic stenosis	6 mo.	–	–
7	F.P	Left ventricular failure hypertension mild aortic stenosis	5 mo.	–	–
8	L.W	Constrictive pericarditis	1 yr	–	–

of severe pulmonary arterial hypertension in the 4 patients in this series the most significant finding in all 4 patients was pulmonary venous hypertension and this is similar to the observations made previously in cases of mitral valve disease with radiologic evidence of ossific nodules.[8] Although a rheumatic pneumonia has been suggested as a precursor of bone nodule formation this clearly does not apply to this group of cases. There was only moderate hemosiderosis histologically and as in mitral valve disease, it did not appear to be related to bone nodule formation The formation of ossific nodules can be explained by postulating osseous metaplasia in areas of organizing intra alveolar edema The intra alveolar edema is caused by pulmonary capillary pressure in excess of the plasma osmotic pressure secondary to a raised pulmonary venous pressure

The rise in *pulmonary venous pressure* can be due to one of several lesions which obstruct forward pulmonary venous flow and this may occur in the pulmonary veins in the left atrium at the mitral valve or in the left ventricle In Case 1 the atrial myxoma caused internal mechanical obstruction to flow at the level of the mitral valve in Cases 2 and 4 the impediment to the circulation was a raised end-diastolic pressure in the left ventricle due to left ventricular failure which in turn produced left atrial hypertension[11, 7] and in Case 3 the constrictive pericarditis caused external obstruction to diastolic filling of the left ventricle by limiting its diastolic expansion thus producing a rise in left atrial and pulmonary venous pressure

Previous authors have suggested an inflammatory basis for bone nodule formation usually in association with pulmonary congestion There was no evidence of either old or recent inflammation in the areas of nodule formation in any of our cases in this series and similar observations were made in those with mitral valve disease.

In cases of mitral stenosis ossific nodules are more common in men than in women. There were 3 males and 1 female in the present series, but no conclusions can be drawn from these selected cases.

Summary

Four cases have been described in which ossific nodules were demonstrated histologically at autopsy in the absence of mitral valve disease. Postmortem contact radiography of lung slices was of assistance in identifying the areas of bone.

All 4 patients had significant pulmonary venous hypertension as assessed clinically and radiologically Pulmonary arterial hypertension was of only moderate severity in 2 patients, and minimal in the other 2.

None of the patients had valvular heart disease and the pulmonary venous hypertension was attributed to internal or external mechanical obstruction to blood flow in 2 patients and to left ventricular failure with a raised ventricular end diastolic pressure in the other 2 patients.

The findings in these 4 patients fit the hypothesis that pulmonary venous hypertension is the critical factor in the pathogenesis of the nodules, as has been suggested in mitral valve disease.

The time required for bone nodules to develop is difficult to assess. Histologically detectable bone can probably form within a period of 6 months from the onset of symptoms and nodules become visible on contact radiography within 12 to 18 months. Three to 5 years may be necessary before bone nodules can be seen on a plain chest film

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Clinical pathologic conference

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Dr Eisenstein The case for discussion today is not a diagnostic problem but is presented as an example of an instance in which a cardiovascular disease is directly related to an endocrine disorder

DR SCHWARTZ It has been said many times and in many places that all diseases are in essence endocrinologic or metabolic and it is gratifying to find that even cardiologists are coming to appreciate this truism The patient whose case is to be discussed today probably had lesions of the cardiac valves only because they were exposed to excessive concentrations of a hormone

Clinical abstract

This 28-year-old white housewif was well until November 1959 when she had hysterectomy and oophorectomy for a dermoid cyst of the ovary Since the age of 17 she had blushed easily (It is unlikely that blushing marks the onset of this patient disease but I would agree that the ability of young girls to blush is becoming increasingly rare.) I reviewing the literature, I was unable to find ny patients i whom dermoid cyst of the ovary and the carcinoid syndrome coexisted, although it is well documented that carcinoid tumors may metastasize to the ovary She recovered well from the operation, but in February 1960, she dev loped weakness night sweats, nausea, diarrhea, pain in both flanks, shortness of breath, and a swollen bdomen. After 3 weeks, she consulted her physician, who admitted her t another hospital where she w told she had "leaky alves. After 3 week of bed rest diuretics, nd digitalis, she lost 30 pounds and was transferred here.

The patient ympt ms nd her response to therapy are, of course, strongly suggesti e of heart failure. This is a rather unusual course for metastatic carcinoid, particularly after a relati ely short period of symptoms.

Physical examination. The blood pressure was 120/70 mm. Hg (Contrary to the often expressed clinical impression the majority of patients with this disorder do not ha e sustained hypertension.) The pulse was 110, respirations were 22 and the temperature was 97°F She was thin and pale with a flushed face and neck, and she had telangiectases of the cheeks, nose, and neck. There were scattered inspiratory râles and some dullness to percussion t the base of the left lung It is not unusual for these patient to ha e asthmatic attacks, but there is no mention here of expiratory wheezes. The heart was not enlarged to percussion but there was rough ejection systolic murmur with a thrill along the left sternal border which extended p into the second intercostal pace and down to the fourth intercostal space followed by short diastolic murmu The abdomen was distended and diff sely tender in both lower quadrants, with a nonpulsating liver palpated 4 fingerbreadths below the cost l margins.

It is difficult to decide whether this patient had thickening of either the tricuspid or pulmonic al es. It would be reasonable to assume that thickening of either one or the other is present lthough the lack of pulsation of the liver is evidence against tricuspid insufficiency I should mention, i passing, that pressure on a liver that contains metastatic lesions of carcinoid often produces haracteristic flush.

Laboratory data. X-ray films of the hest, esophagus, stomach, small intestine, and colon ere normal. Hemoglobin 11 1 Gm. per cent whit blood cell ount, 9 400 per cubic millimeter with 35 per cent poly 37 per ent bands, and 28 per cent lymphocytes. Urinalysis was negati e. Alkaline phosphatase A/G ratio, nd bilirubin in the serum all were normal. Bromsulphalein retention wa 26.5 per cent Urine 5-hydroxy indole-acetic acid was

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263 μg per 24 hours (normal, 2 9 μg). Serum serotonin, 1 4 μg per milliliter (normal, 0.09-0 18). Serum 5-hydroxy indole-acetic acid, 1 45 μg per milliliter (normal, 0.5). The Bromsulphalein retention may reflect both tumor invasion and passive congestion of the liver One should also consider the possibility of hepatic cirrhosis because of the propensity of these tumors to stimulate fibrosis. The urine 5-hydroxy indole-acetic excretion seems to have been extraordinarily high even for a patient ith metastatic carcinoid, unless, perhaps, the patient subsisted entirely on bananas.

Hospital course. While in the hospital the patient had periodic flushes. On the tenth hospital day celiotomy was performed. A primary tumor was removed from the mid-small bowel. Many metastases were found in the liver and lymph nodes. The histology was that of carcinoid tumor Postoperatively she had few episodes of tightness in the chest, dyspnea, flushing cyanosis, and expiratory wheezes. It is interesting that, t this juncture, the patient did have evidence of bronchiolar constriction. She was discharged 3 weeks after operation on 100 mg of isonicotinic acid hydrazide, four times day I am not ware of published reports of the use of isonicotinic acid hydrazide in the treatment of this disorder but Dr Oglesby Paul tells me that its use was suggested by Dr Francis Wood, of the University of Pennsylvania. At any rate, it was Dr Paul' impression that after ts institution there seemed t be moderate but definite reduction in the frequency and severity of the attacks of flushing

The patient was hospitalized 1 year later having shown little improvement in her endocrine symptoms, except for a little less flushing The entire skin was now dusky red, but it blanched on pressure, and the periphery of the tongue was the same color There was 2 plus peripheral edema. There were physical and -ray findings of bilateral pleural effusion. Her condition had obviously deteriorated great deal, with wasting still larger liver tense abdomen, and distended neck veins. After several thoracenteses, celiotomy was performed in the hope that enough tumor could be removed to relieve some of the symptoms. During the operation large cyst on the liver was found, which ruptured. Shortly afterward, the patient blood pressure became unobtainable and she died.

DR. SCHWARTZ The patient s course was shorter than the average but one could hardly take issue with the decision to attempt surgical removal of tumor tissue in a patient whose condition clearly was deteriorating rapidly I would like to emphasize, however that many of these patients *survive for long periods after the diagnosis* is made, and in some the symptoms may be rather minimal consisting of nothing more than the discomfort of three or four bowel movements a day and occasional attacks of flushing I should also mention that the basic tenets of clinical medicine apply even to the care of patients with this bizarre and dramatic disease. I have in mind a patient recently seen who had well-documented hyperfunctioning carcinoid tumor with hepatic metastases. The patient was referred because of intractable diarrhea. It became clear on examination that she had aside from the absence of eye signs, classic Graves disease. Treatment with radioiodine resulted in a gain in weight of more than 20 pounds, and bowel movements were reduced from as many as 25 to an average of 4 per day The diagnosis of metastatic carcinoid tumor does not carry with it any immunity to other diseases, and indeed since there is some evidence that serotonin stimulates glucose oxidation in the thyroid gland[1] it is conceivable that patients with hyperfunctioning carcinoid tumors have an increased susceptibility to thyrotoxicosis.

Since this unfortunate woman s condition can hardly be considered to be a diagnostic problem, the remainder of the discussion will be devoted to the carcinoid syndrome. Let us begin by viewing the disease in physiologic terms. The biochemical anatomy of the pathway of production and disposition of serotonin are now well known and the major reactions may be indicated by the following sequence tryptophan→ 5-hydroxytryptophan→ 5-hydroxytryptamine (serotonin)→ 5-hydroxy indole-acetic acid Thus, starting from a common amino acid tryptophan serotonin is formed it is then inactivated partly through the action of an important enzyme monoamine oxidase to the inactive excretion product, 5-hydroxy indole acetic acid To move to the organ level serotonin is normally produced by argentophilic tissues, predominantly in the gut. For this reason most of the hormone passes through the portal circulation to the liver before it has access to peripheral tissues. The liver is a potent inactivator of serotonin so that in the normal individual relatively little hormone reaches the peripheral circulation *Indeed it is debatable whether there is any free serotonin present in plasma.* However sizable quantities are firmly bound to blood platelets, and appreciable quantities are present in the central nervous system where it may function as a transmitting agent *analogous to compounds such as* acetylcholine When blood platelets are

disrupted as in the case of burns or anaphylactic shock, serotonin is released and is then free to act on small blood vessels. The nature of this action is on a clinical level at least confusing since it seems to provoke both arteriolar constriction and dilatation It may well be that concomitant release of epinephrine norepinephrine and histamine is involved and these together with change in autonomic function obviously would tend to obscure the primary effects of serotonin

With this meager background then we can move on to the full blown clinical picture of metastatic carcinoid which is fairly well typified by the patient whose case is under discussion today It should be mentioned at the onset that a carcinoid tumor of the appendix and small bowel is not a rare finding and perhaps one quarter of these may metastasize Only in about 1 per cent of the cases however does the hyperfunctioning carcinoid syndrome appear

The clinical manifestations may be conveniently divided into three categories. The first is referable to changes in the skin including the facial telangiectasia, as noted in this patient the episodes of flushing and the plethoric appearance accompanied by areas of patchy cyanosis. The second category is that of the phenomenon of constriction of smooth muscle, with asthmatic wheezes resulting when bronchioles are affected dyspnea resulting from pulmonary vasoconstriction and perhaps, hypertension from renal arteriolar constriction The third category stems from the peculiar extensive fibrosis which appears in areas exposed to high concentrations of serotonin. This is quite striking in those instances in which ovarian metastases have occurred In some patients a "frozen pelvis" results. It is also a major factor in the genesis of the thickened tricuspid and pulmonic valves which have appeared in these patients. The striking preponderance of valvular lesions on the right side of the heart has given rise to the hypothesis that peripheral manifestations of hyperfunctioning metastatic tumors of the gut are ordinarily *prevented or greatly mitigated* by the liver's sizable capacity to inactivate serotonin. Venous drainage from hepatic metastases, however is not subject to this screening-out influence so that large quantities of serotonin may be delivered to the right side of the heart, presumably stimulating fibrosis of the tricuspid and pulmonic valve leaflets. Since the pulmonary parenchyma also is rich in monoamine oxidase activity it consequently may serve to inactive excessive quantities of serotonin Ovarian metastases may also provoke peripheral manifestations, since in this case the liver is bypassed so that the ovarian blood drains directly into the right side of the heart.

Although the classic features of the carcinoid syndrome are now well established case reports of new variants in the clinical picture have been appearing These could be grouped as follows (1) Carcinoid tumor—both clinically and chemically inactive the usual neoplasm of the appendix falls into this category (2) Carcinoid tumor—chemically active but clinically inactive there are a few patients who have elevated levels of blood serotonin and urinary 5-hydroxy indole acetic acid but manifest none of the clinical symptoms of the carcinoid syndrome (3) Carcinoid tumor—chemically and clinically active such as in the patient whose case is under discussion (4) Metastatic bronchial adenoma—in a few cases (9 at last count) there were elevated levels of blood serotonin and associated symptoms. These tumors are not always argentophilic indeed in one patient the pathologic lesion apparently was an oat-cell carcinoma of the lung (5) Multiple endocrine tumors. In two instances carcinoid tumors were found in association with acromegaly and one wonders whether carcinoid should be added to the symptom complex of multiple endocrine adenomata.

Treatment of the carcinoid syndrome can be described only as unsatisfactory A variety of serotonin antagonists including lysergic acid derivatives have not been very helpful. Alpha methyl-dopa which blocks the conversion of tryptophan to 5-hydroxy tryptophan did not affect beneficially the discomforting flushes or the excretion of 5-hydroxy indole-acetic acid Instead it provoked a black tongue and prostration. Compazine may provide symptomatic relief In sum medical treatment is highly rational but essentially unsuccess-

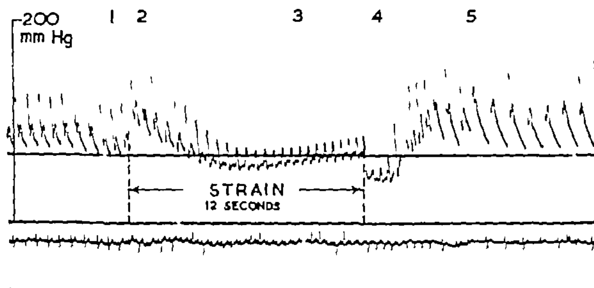


Fig. 1. The brachial arterial pressure recorded continuously before, during and after release of the Valsalva maneuver in a normal subject. The phases of the response are numbered 1 through 5. See text for discussion.

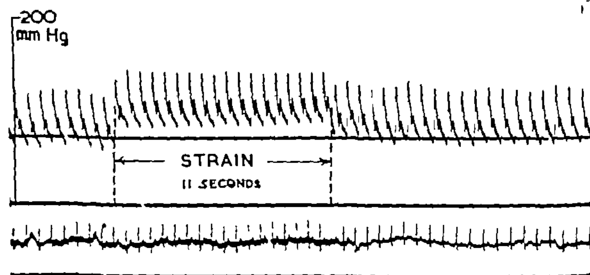


Fig. 2. The brachial arterial pressure recorded continuously before, during and after release of the Valsalva maneuver in a patient with large uncomplicated atrial septal defect without heart failure. The response is of the square wave or "heart failure" type. See text for discussion.

3 consecutive beats with the highest systolic pressure during the period after release of the strain (referred to as the "systolic overshoot") and (4) the average heart rate of the 3 consecutive beats with the slowest heart rate in the period after release of the strain (referred to as the "overshoot bradycardia").

Results

Normal subjects. Normal subjects regularly showed the previously described response. However, the quantitative response to a standard Valsalva maneuver has not been reported previously in adequate detail and we found it to be more variable than is generally thought. During



Fig. 1. Mesenteric lymph node. The typical histology of carcinoid tumor is seen.

ful. On the other hand, surgical treatment seems barbaric in contrast but, at this time, appears to offer the best chance of relief to the patient. It consists of the excision of as much metastatic tissue as possible and, thus, the removal of the source of excessive serotonin. Since in many patients the tumor, including metastases, grows quite slowly, this drastic form of treatment may have real merit.

DR. PAUL. The use of isonicotinic acid hydrazide is based on a report that the drug reduces the synthesis of serotonin by carcinoid tumors, with a resultant fall in blood and platelet levels of serotonin. In this patient, diarrhea and flushing became less severe after use of the drug.

DR. EISENSTEIN. Dr. Hector Battifora performed the autopsy and there were no surprises. The anatomic changes were those which have become the classic picture of the carcinoid syndrome. The tumor itself was widespread in the abdominal cavity, with massive involvement of the liver, the serosa of the ileum, and the lymph nodes of the mesentery of the small intestine. The histology was that of a carcinoid tumor (Fig. 1). The cytoplasm of the tumor cells stained with the argentaffin reaction and diazonium salts. This may be of pharmacologic importance since there seems to be some evidence that these staining reactions are correlated with pharmacologic activity of these cells.[3] The cyst which the surgeon opened was a mass of necrotic tumor 15 cm. in diameter (Fig. 2). Fluid from an adjacent similar cyst contained 1.71 μg per milliliter of serotonin and 100.1 μg per milliliter of 5-hydroxy-indole-acetic acid. It was several hours between the time the patient died and the time the tissue was frozen, so that the true amount of serotonin present during life was probably much higher. This patient may have died of acute serotonin poisoning when the cyst was ruptured during the operation.

Almost all the other anatomic findings of significance were part of a diffuse fibroblastic process which all the evidence indicates is a pharmacologic effect of the tumor. The best known of these lesions is in the heart. In this patient the heart weighed only 250 grams, but it showed widespread endocardial sclerosis. The endocardium of the right atrium was studded with numerous indurated white plaques which became confluent near the atrial appendage, and here the organ was so indurated that it maintained its shape after sectioning. The tricuspid valve was stenotic and insufficient, with an orifice large enough to admit only two fingers. The right ventricle was dilated. The pulmonic valve cusps



Fig. 2. Liver. There are many necrotic, cystic masses of tumor replacing liver parenchyma.



Fig 3 Pulmonic valve The valve is transformed into thick leathery diaphragm with an orifice 0 7 cm. in diameter

were thick and fused so that the valve formed a thick relatively immobile diaphragm with a central orifice only 0 7 cm. in diameter (Fig 3) The mitral valve was also affected with thick rolled edges and short sometimes fused chordae tendineae. It did not appear to be stenotic Apparently then the circulating factors responsible for the fibrosis were in high enough concentration so that they were not completely degraded in the lung and were able to affect the left side of the heart. The other two locations at which fibrous tissue proliferation was found were in the intima of the vena cava near the orifice of the hepatic vein and in the peritoneal cavity particularly the pelvis where the parietal peritoneum was as thick as 3 mm and had a cardboard like consistency (Fig 4)

Histologically these areas of proliferative fibrosis were composed of large masses of collagen often laminated with scattered interspersed fibroblasts. Collagen was virtually the only extracellular material that was present. The lesions were basically similar whether they were endocardial vena caval or peritoneal Scattered foci of lymphocytes were found in the interstitial tissue of the left ventricle (Fig 5) This is of interest since myocarditis has been described in patients with pheochromocytoma —a tumor which secretes a quite different but also profoundly vasoactive hormone.

DR. BATTIFORA Is it safe to assume that serotonin is the chemical agent which stimulates the proliferation of fibrous tissue in this syndrome?

DR. EISENSTEIN There have been numerous attempts to reproduce the valvular lesions by administration of serotonin[4] To my knowledge, none has been successful It has been noticed however that there is a severe dermal fibrosis when this compound is injected subcutaneously

DR. HASS There is another rather intriguing chemical relationship here The auxins which are plant growth hormones, include indole 3-acetic acid Indoles appear to be co-carcinogens in some chemically induced tumors in rats, and the fibrotic lesion in

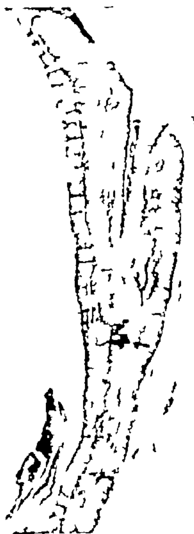


Fig 4 Adrenal gland The capsule is thickened by mass of dense collagenous connective tissue

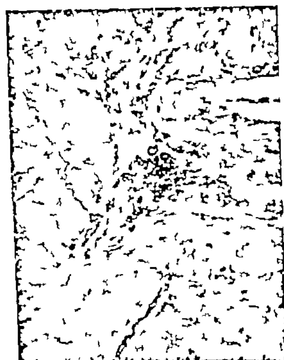


Fig. 5 Left ventricle. There is a collection of lymphocytes in the perivascular stroma.

the carcinoid syndrome is basically a proliferative cellular response. Serotonin is not the only compound circulating in excess concentration in this disease. As is clear in this patient the concentration of other indolic compounds in the blood such as 5-hydroxy indole-acetic acid is much higher than that of serotonin It is barely possible that the experimentalists have been injecting the wrong thing

DR. AYER Is the physiologic function of serotonin known?

DR. EISENSTEIN I do not believe so although its pharmacologic effects are profound It has been thought to play a role in such varied things as hemostasis antidiuresis constriction of smooth muscle allergic reactions, and the transmission of nerve impulses. For a while a few years ago it almost replaced the pineal gland as the seat of the soul In rats, at least it is interesting that tolerance develops to the drug In some experiments I did some time ago the dosage required to induce flushing increased rapidly after a few days of injections. To put a word in for a wise pathologist, Masson many years ago suggested on morphologic grounds that argentaffin cells were neuroendocrine in nature.

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Fundamentals of clinical cardiology

Assessment of functional recovery of men surviving first myocardial infarction

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The outlook after recovery from myocardial infarction was little known and was viewed pessimistically some 30 years ago Prolonged convalescence and postponement of return to ordinary life as long as possible were recommended in 1938 Rehabilitation and return to work were not mentioned at a symposium on coronary artery disease in 1930 In 1934 a meeting of the Royal Society of Medicine [illegible]cluded that there was insufficient evidence for any assessment of long term prognosis During this period observant physicians were describing patients who lived and worked many years after an infarction Some adventurous patients ignored restrictions and resumed vigorous lives

McMichael and Parry[4] in 1960 reviewed the more important follow up studies of those recovering from a single infarction and found 5-year survival rates about 65 per cent They concluded that chances of survival after acute infarction can be assessed by consideration of age sex economic status severity of the attack and degree of recovery and complicating diabetes and hypertension Authors agree that patients returning to full activity have 5-year survival rates around 80 per cent

In 1940 the New York Central Railroad Medical Department adopted a policy of returning operating personnel to full time work after myocardial infarction if examination by an internist indicated a good functional recovery This report is concerned with the fate of 348 men who applied for return to service after initial infarction and some clinical observations influencing the prognosis

Materials and methods

Of 348 men who applied for return to service 292 resumed full time work and 56 were recommended for retirement Those selected for this study had characteristic electrocardiograms and a definite clinical history and date of onset of infarction Engineers were routinely and permanently restricted to yard assignments Since restrictions which had usually been accepted initially were sometimes disputed subsequently it was the responsibility of the medical director to obtain electrocardiograms taken during the acute attack if the railroad company's electrocardiograms were inconclusive

All men had pre-employment and routine periodic examinations preceding the first infarction Those returning to work after infarction were re-examined as recommended by the internist This was usually at intervals of 3 to 6 months during the first years and at intervals of 6 to 12 months in those who survived many years without symptoms or further disability The initial infarcts occurred between July 1 1940 and July 1 1957 and all men were followed until July 1 1962

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During the rehabilitation period after the acute infarction these men were expected to proceed through a program of progressive exercise under the guidance of their personal physicians. It was required that this program bring them to a level of activity roughly equivalent to that of their ordinary duties without disabling symptoms. Those lacking such rehabilitation were held off work additional weeks in order to increase their exercise tolerance. The time from the date of the initial infarct to resumption of work is shown in Table I Those off work over a year usually had taken disability retirement but applied for return to service as incapacitating symptoms gradually subsided With the exception of engineers most employees returned to their usual work.

A modified double Master test has been employed in the medical director's office to estimate the adequacy of the coronary circulation. The test is seldom used at the first return-to-service examination since most men have not attempted a spurt of maximum exercise during the rehabilitation period It is avoided if preinfarction angina is suspected The test is used in men actively employed who describe mild angina that is not considered to be incapacitating or who develop nonspecific S-T segment or T wave changes suggestive of myocardial ischemia without symptoms. Those with ischemic response are usually continued at work after consideration of their symptoms and duties. They are followed closely and some are restricted to easier assignments. A few with ischemic responses of 2 mm or more have been temporarily removed from service and referred to their attending physicians.

Some men have been examined periodically with routine chest x-ray films and often fluoroscopy In many these studies were made only if clinically indicated Men who retired after 65 years of age were classified as retiring because of age regardless of health Obese and diabetic men in this series were too few to be of consequence Only one man has been treated with long term anticoagulation after the first infarction and 4 have been similarly treated after second infarctions.

The causes of death and incidence of recurrent infarctions were determined by re-examinations reports from attending physicians death certificates and records of the United States Railroad Retirement Board For those who died suddenly the diagnosis of myocardial infarction on the death certificate was accepted and these men are included in the group described as having recurrent clinical infarctions.

Table I Time from initial infarction to resumption of work

Time	Number
Under 3 mo.	36
3 6 mo.	180
6 to 12 mo.	58
Over 1 yr	18

Results

On July 1 1962 162 men of the 292 who resumed work were living and 84 were still actively employed. Sixty-six retired in the usual manner between ages 65 and 70 Seventy-four retired for disability before 65 The causes of death and disability are given in Tables II and III Further manifestations of coronary heart disease predominate as causes of death or disability in men who made a good recovery from the initial infarction

The 97 fatal recurrent clinical infarctions were second attacks in 77 third attacks in 19 and a fourth attack in 1 The time interval between onset of symptoms and death in the final attack is known in 35 Fourteen died within 1 hour and another 15 died within 24 hours. Attending physicians may be more likely to report this interval in dramatically sudden deaths, but it can be concluded that many men who die of recurrent clinical infarction do so suddenly or relatively suddenly Fifty-six of these fatalities occurred in men actively employed All happened on off-duty hours or during sick leave although 3 men died suddenly shortly after completing a trip These findings indicate that work for which men have been conditioned and to which they have become accustomed is not a factor in death from coronary heart disease.

Table II. Causes of 130 deaths after return to work

Cause	Number
Recurrent clinical myocardial infarction	97 (75%)
Congestive heart failure	14
Malignancy	7
Cerebral vascular accident	2
Miscellaneous	3
Unknown	7

Table III. Causes of 74 disability retirements after return to work

Cause	Number
Angina pectoris	33
Recurrent infarction	13
Congestive heart failure	10
Miscellaneous	10
Cerebral vascular accident	5
Malignancy	3

Five years after the first infarction in the 292 men who returned to work, 52 (18 per cent) were dead, 74 (25 per cent) had a second clinical infarction, and 30 (10 per cent) were living but retired for disability. Thirty-nine of the second clinical infarcts (53 per cent) were fatal.

One hundred and forty-six men who returned to work were followed 10 years or more. Ten years after the initial infarct, 85 (58 per cent) were living, 65 (45 per cent) had a second clinical infarct, and 15 (10 per cent) were living but medically retired. Of the 65 second infarcts, 35 occurred in the first 5 years after initial infarction, with a mortality rate of 46 per cent, and 30 additional second infarcts occurred in the second 5 years, with a mortality rate of 77 per cent.

Fifty-six men who applied for return to service after the first myocardial infarction were recommended for retirement. The reasons for this recommendation and the 5-year survival rates in relation to these reasons are listed in Table IV. Thirteen of these men, who were thought to be able to return to restricted work, elected to apply for retirement benefits. Fifty-five per cent of those who retired after the initial infarct lived 5 years or more. Cardiomegaly after the first infarction was the only reason for medical retirement associated with a significantly low 5-year survival rate.

Angina pectoris. Only 18 men who returned to work had angina for 3 months or more preceding their first infarction. This emphasizes that the onset of angina in men should arouse suspicion of acute or impending infarction. One third of these 18 men had relief of angina after the first infarction, and in the remainder it persisted.

Angina is the most common cardiac symptom after good recovery from the first infarction. Dyspnea is infrequent and rarely impressive. Seventy-one men who applied for return to service described persistent classic angina after recovery from their initial infarct. In 20 of these, without measurable cardiomegaly, the angina was considered to be so severe and frequent that it would be precipitated often by their ordinary duties, and these men were recommended for disability retirement. In 51 men who returned to work, the angina was mild, infrequent, and predictable to the extent that it could be avoided usually by minimal restriction of ordinary activities. Over half of these 51 men had their rehabilitation after the first infarction prolonged by more severe angina, but the chest pains had largely subsided when they were examined for return to work.

McMichael and Parry[4] found differences of opinion in regard to the prognostic significance of postinfarction angina. Angina

Table IV. Five-year survival in relation to reason for medical retirement after first myocardial infarction

Reason for retirement	Number	Lived 5 years or more
Angina without cardiomegaly	20	10 (50%)
Personal choice	13	10 (77%)
Associated disease	12	8 (66%)
Cardiomegaly	9	1 (11%)
Hypertension without cardiomegaly	2	2 (100%)

Table V Five year prognosis in relation to postinfarction angina

Type of angina	*Number*	*Lived 5 years*	*Had second clinical infarct within 5 years*	*Mortality rate of second infarct*
Disabling without cardiomegaly	20	10 (50%)	—	—
Mild angina	51	39 (76%)	16 (31%)	10 (62%)
Denied angina	241	201 (83%)	58 (24%)	29 (50%)

Table VI Five year prognosis in relation to age at first infarction

Age at onset (yr)	*Number*	*Lived 5 years or more*	*Had second clinical infarct within 5 years*	*Mortality rate of second infarct*
30–39	11	11 (100%)	3 (27%)	0
40–49	68	56 (83%)	18 (26%)	10 (55%)
50–59	145	124 (86%)	38 (26%)	19 (50%)
60–69	68	49 (72%)	15 (22%)	10 (66%)

Table VII Ten year prognosis in relation to age at first infarction

Age at onset (yr)	*Number*	*Lived 10 years or more*	*Had second clinical infarct within 10 year*	*Mortality rate of second infarct*
30–49	36	26 (72%)	14 (44 [illegible])	6 (43%)
50–59	74	43 (58%)	34 (46%)	18 (53%)
60–69	36	16 (44%)	17 (47%)	15 (88%)

has a variable course but in these men with a strong desire to work men with angina which was considered to be disabling for full time work had a significantly increased 5 year mortality rate in comparison to those who returned to work free of chest pains. Mild angina did not have significant prognostic implications (Table V)

Cardiac enlargement Measurable cardiac enlargement (transverse diameters of the heart more than half the inside transverse diameter of the chest) was detected in 16 of the 348 men who applied for return to work. Nine usually with mild angina or exertional dyspnea were recommended for medical retirement and only 1 lived 5 years. Seven who denied symptoms returned to work and 4 lived 5 years.

In 8 men cardiomegaly was attributed to a history of congestive heart failure which complicated the acute infarction or the rehabilitation period One of these 8 had a ventricular aneurysm In the other 8 men the enlargement was attributed to fixed diastolic hypertension which preceded the first infarction The 5 men who survived 5 years all had enlarged hearts on the basis of hypertension The most adverse single prognostic sign in this study is measurable cardiac enlargement attributable to congestive heart failure which complicates the initial infarction.

Age McMichael and Parry[4] indicated that prognosis worsens with increasing age. Honey and Truelove found that those over 60 years old who made a good recovery from an infarction had about the same outlook as the general population over 60. In those under 60 death rates exceeded normal expectations about three times within 5 years usually due to re

Table VIII Five year prognosis in relation to electrocardiographic residuals 1 year after acute infarction

Residual	Number	Lived 5 years or more	Had second clinical infarct within 5 years	Mortality rate of second infarct
Returned to normal	28	24 (86)	4 (14%)	3 (75%)
Remained abnormal	243	201 (80%)	64 (26%)	31 (48%)
Fixed acute pattern	21	15 (71%)	6 (30%)	5 (83%)

Table IX Ten year prognosis in relation to electrocardiographic residuals 1 year after acute infarction

Residual	Number	Lived 10 years or more	Had second clinical infarct within 10 years	Mortality rate of second infarct
Returned to normal	15	12 (80%)	2 (13%)	1 (50%)
Remained abnormal	123	71 (58%)	58 (47%)	34 (59%)
Fixed acute pattern	8	2 (25%)	5 (62%)	4 (80%)

Table X Five year prognosis in relation to hypertension

Factor	Number	Lived 5 years or more	Had second clinical infarct within 5 years	Mortality rate of second infarct
Fixed diastolic hypertension	26	16 (61)	10 (39%)	8 (80%)
No hypertension or labile type	266	224 (84)	64 (24%)	31 (48%)

current infarction The 5 and 10-year prognosis in relation to age in this study is indicated in Tables VI and VII The differences are not of statistical significance except that in men over 60 the second infarcts which occur in the fifth to tenth year after the first infarction are more likely to be fatal

Electrocardiographic residuals McMichael and Parry found that most authors did not consider the electrocardiogram to be helpful in estimating prognosis They suggested that a normal record is a good sign Of the 292 men who returned to work 28 had electrocardiograms which returned to normal within 1 year after the acute attack Nineteen of these originally had shown electrocardiographically small posterior infarctions. Two hundred and forty three tracings remained abnormal and 5 of these showed bundle branch block Twenty-one records persistently exhibited a fixed pattern of acute infarction and Myers and associates found that such a pattern indicates extensive destruction and fibrous replacement of the ventricular wall sometimes leading to ventricular aneurysm

The 5 and 10-year prognosis in relation to electrocardiographic residuals is shown in Tables VIII and IX Clinically mild infarctions with minor electrocardiographic changes, frequently posterior in location are too often the forerunner of fatal recurrent infarctions. Those men with initial small posterior infarcts who escape a second infarction have the best 10-year prognosis. A fixed pattern of recent infarction indicates scant chance of surviving a second clinical infarction.

Hypertension McMichael and Parry[4] concluded that hypertension particularly when complicated by cardiac enlargement or severe retinal changes shortened the

survival prospects. In this series, 26 men who returned to work had fixed diastolic pressures above 90 mm Hg before or after the first infarct. All those who developed a fixed hypertension after their infarction had a labile type preceding the infarct. Six men had been closely observed for hypertension and had measurable cardiac enlargement before their first infarction. Table X indicates that fixed diastolic hypertension particularly when of sufficient severity and duration to cause measurable cardiac enlargement significantly impairs the 5-year outlook.

Electrocardiographic exercise test. Fifty three men were examined with an exercise test before July 1 1957 The differences in Table XI are not of statistical significance The test is sometimes of value in detecting transient coronary artery insufficiency but has no value in predicting recurrent infarction in a group with known old infarction

Ventricular aneurysm. Two ventricular aneurysms were detected in those who applied for return to service. One man with generalized cardiac enlargement and a history suggestive of recurrent congestive failure was recommended for retirement and died of chronic failure 4½ years after his acute infarct The other man 42 years old without generalized cardiac enlargement or symptoms returned to work. He was intermittently disabled by angina and recurrent *failure* and died suddenly 5½ years after his initial attack. One man still working has had paradoxical pulsations in the anterior ventricle for 9 years without developing an aneurysmal sac or generalized enlargement.

Three aneurysms were found on re-examinations in men returned to work. One was discovered after compensation from an episode of congestive failure a year after acute infarction This man remained compensated but had progressive cardiac enlargement and died suddenly 5½ years after his acute infarction. An apical aneurysm with a rim of calcium in its wall was detected 8 years after the acute infarction in a man who developed chronic failure he died suddenly 1½ years after retirement. An asymptomatic aneurysm was found in a man 2 years after he had returned to service he died suddenly 2 years after this finding and death was reported to be due to acute infarction complicated by a saddle embolus.

All men with aneurysms had an electrocardiogram of fixed pattern of acute infarction in the anterior leads. No posterior wall aneurysm was recognized in this series. Development of an aneurysm after the first infarction has an adverse effect on the prognosis. Aneurysms must be searched for particularly when the electrocardiogram persists in resembling recent infarction. Men with aneurysm complicating the acute infarction may make a good functional recovery but if they are returned to work job placement must be carefully considered and re-examinations must be frequent.

Table XI. Response to exercise and incidence of recurrent infarction and death 5 years after test

Response to exercise	*Number*	*Had second clinical infarct*	*Dead*
Ischemic	22	9 (41%)	8 (36%)
Negative	31	13 (42%)	8 (26%)

Discussion

Keys estimated that among middle aged men in this country the annual incidence of new coronary heart disease is about 1 per cent. In this study approximately 5 per cent of the men who returned to work were *subject to second clinical* infarction annually during the first 5 years after the initial infarction and about half of these second infarcts were fatal Practically all of these second attacks occurred unexpectedly This unpredictable nature of the disease and the increased susceptibility to infarction justify restriction to work where sudden death or disability will not be hazardous to others.

Most men who make a good recovery after a single infarction will have eventually further evidences of coronary heart disease but the majority have many years of symptom free, productive life between the first and final manifestations of the disease. In some the final attack comes after age 70 Men with a *strong desire to*

work should have that privilege, and management and labor should join in creating job opportunities for men who make a good recovery from myocardial infarction. With such conditions, men with adverse findings of hypertension, mild postinfarction angina, severe electrocardiographic residuals, or ischemic responses to exercise can return safely to appropriate work and be followed closely. Exploitation of the natural history of the disease by management, labor, or litigants makes this optimistic view impossible.

Measurable cardiac enlargement attributable to congestive heart failure which complicates the acute infarction or hypertension, severe persistent angina, and ventricular aneurysm are strong indications for retirement despite the patient's determination to return to full-time vigorous work.

Summary

The subsequent histories of 348 men who applied for return to full-time railway operating service after their first myocardial infarctions have been described. Two hundred and ninety-two returned to work, and 5 years after initial infarction 83 per cent were living, 25 per cent had sustained a second clinical infarction, and 10 per cent were living but medically disabled. One hundred and forty-six men who returned to work were followed 10 years or more. Ten years after initial infarction, 58 per cent were living, 45 per cent had had a second infarction, and 10 per cent, although living, were medically disabled. Recurrent myocardial infarction was the major cause of death, and disability was largely due to angina or recurrent infarction. Of 56 men recommended for disability retirement after the first infarction, 55 per cent lived over 5 years.

Measurable cardiac enlargement attributable to congestive heart failure which complicated the first infarction was the most adverse single prognostic sign in this series. Hypertension, particularly when accompanied by cardiomegaly, severe and persistent angina, and a fixed electrocardiographic pattern of acute infarction sometimes associated with a ventricular aneurysm significantly shortened the prospects for long survival. Age was of little importance in this study, although men who were near 70 years old did not survive a second infarction as often as did younger men. The electrocardiographic exercise test, sometimes helpful in detecting transient coronary artery insufficiency, was not a prognostic guide in this group. Men whose electrocardiograms returned to normal, although not free of recurrent infarctions, had the best long-term outlook.

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the strain the pulse pressure narrowed by an average of 52 per cent (range 10 to 78 per cent) and this was accompanied by an average tachycardia 42 per cent above the resting heart rate. The systolic overshoot reached an average of 29 per cent above the resting systolic level (range 5 to 56 per cent) and was accompanied by an average bradycardia 27 per cent below the resting heart rate (range, 11 to 45 per cent) Every subject showed a change of at least 15 per cent in either pulse pressure during the strain or systolic pressure during the overshoot.

In the 30 normal subjects studied without arterial puncture, the heart rate responses were similar although on the whole were less marked. There was an average tachycardia during the strain of 35 per cent, but this varied widely from 2 to 75 per cent. The average overshoot bradycardia was 19 per cent (range 0 to 50 per cent) Every normal subject showed at least a 10 per cent change in heart rate during either the strain or the overshoot period

Atrial septal defect Patients with atrial septal defect were as a group markedly abnormal in all four aspects of the Valsalva response. The average tachycardia during the strain was 12 per cent, less than one third of the normal average the average overshoot bradycardia was only 2.4 per cent or one tenth of the normal average. Pulse pressure narrowed during the strain by an average of 16 per cent, or about one third of the average normal the average systolic overshoot was less than one third of normal at 9 per cent. However the pattern was typically square wave showing less than 5 per cent change in pulse pressure or heart rate, in only 5 of 32 cases most were intermediate abnormal patterns, and the range of the individual measurements showed great overlap with the normal range. The most consistently abnormal measurement was the overshoot bradycardia which was absent in 19 of 36 cases and was less than 6 per cent in 24 of 36 whereas only 2 of 50 normal subjects showed less than 6 per cent overshoot bradycardia. There was a tendency to more abnormal responses in those with larger left to-right shunts (Figs. 3 and 4)

The best separation of patients with atrial septal defect from normal subjects by the Valsalva response was obtained by use of the following criteria of normal (1) The strain tachycardia and overshoot bradycardia are both measurably present and one or the other is at least 10 per cent above or below the resting heart rate. (2) Narrowing of the pulse pressure during the strain and a systolic overshoot after release are both present and one or the

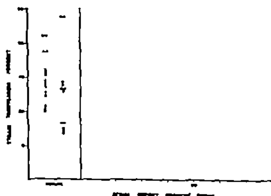


Fig 3 The degree of tachycardia during the strain of the Valsalva maneuver expressed as the per cent increase over the resting heart rate, in 35 patients with atrial septal defect, plotted against the size of the left-to-right shunt, in per cent of pulmonary blood flow *On the left,* The same measurements in 50 normal subjects studied with arterial puncture (*open circles*) or without arterial puncture (*solid circles*).

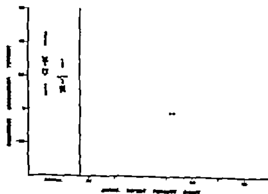


Fig 4 The degree of bradycardia during the overshoot after release of the strain in the Valsalva maneuver in 35 patients with atrial septal defect, expressed as the per cent decrease from the resting heart rate, plotted against the size of the left-to-right shunt, in per cent of pulmonary blood flow *On the left,* The same measurements in 50 normal subjects, studied with arterial puncture (*open circles*) or without arterial puncture (*solid circles*).

Appraisal and reappraisal of cardiac therapy

The neurotoxic effects of digitalis

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From the time that Withering introduced digitalis to the medical profession, the close relation between its neurotoxic and its cardiac effects has been apparent. It has been noted that the various effects of the digitalis glycosides on the central nervous system may occur before, simultaneous with or after other signs of cardiac toxicity

A wide variety of effects on the central nervous system have been described These include blurred vision yellow or green or flickering vision amblyopia, and scotomata. Less well localized symptoms, such as drowsiness, restlessness, weakness, and headache may also occur More extreme effects on the central nervous system, such as hallucinations, seizures delirium and even coma, are seen only occasionally Several authors have reported peripheral and trigeminal neuralgias and paresthesias. All these are readily reversible by withdrawal of digitalis. Neurotoxicity is common in one series of toxic patients, 41 per cent had neurotoxicity with or without other signs. Moreover it has been found that much of the anorexia nausea, and vomiting produced by digitalis is central rather than local in origin. If these symptoms are included in the estimation of the frequency of the effect on the central nervous system then neurotoxicity is by far the most common manifestation of digitalis overdosage.

Despite a mass of clinical experience and descriptive data, detailed pharmacologic and physiologic information concerning the relationship of these effects on the central nervous system to the cardiac effects of digitalis is incomplete, and there is considerable confusion about the clinical implications of neurotoxicity Most physicians consider that signs of toxicity to digitalis in any organ system are a contraindication to continued administration of the drug Nonetheless, it is occasionally suggested that toxic signs be ignored or suppressed in order to give more digitalis to a patient in whom a greater therapeutic effect is urgently desired.

Two pharmacologic questions are implied in this confusion. First, is there likely to be a significant dissociation between neurotoxic and cardiotoxic effects? Second is additional therapeutic effect likely to be observed after the onset of neurotoxic symptoms?

Distribution of digitalis Some knowledge of the distribution of digitalis is essential to a discussion of the first question Studies with C_{14}-labeled digitoxin, with tritiated digoxin and with unlabeled digitoxin by bioassay have shown that digitalis is widely distributed throughout the body and that the heart neither receives a disproportionate amount nor retains it an exceptionally long time.

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The liver binds the largest amount and very considerable amounts are found in the gastrointestinal tract and the kidney. Quantitative differences among the various methods of study are considerable but one author reported that the heart bound only 1 per cent of an administered dose. Species differences have been noted. Digitalis and its metabolites persist in the cat heart but little or no fixation is found in the rat heart.

In view of this wide distribution and species difference it is *not* surprising that evidence of dissociation between neurotoxic and cardiotoxic effects has been found in the laboratory. Thus the presence of a sugar side chain on the cardiac glycoside *consistently reduces neurotoxicity*. Digitoxigenin without a sugar component produces convulsions in cats at doses at which digitoxin would be ineffective whereas digitoxin produces lethal cardiac toxicity in the same animal at a lower dose than digitoxigenin. Also there are glycosides not derived from digitalis that produce effects on the central nervous system only. As could be expected from the fixation data presented above the rat is relatively insensitive to the cardiac effect of digitalis but can manifest neurotoxicity.

Despite these differences, however, both laboratory and clinical evidence suggest that in man and with the glycosides ordinarily used distribution and susceptibility are such that cardiotoxic and neurotoxic effects will occur at very similar doses of digitalis. Confirming this a recent study showed that serial deliberate digitalis intoxications in the same patients with the same glycoside might produce cardiac signs on one trial and central nervous-system signs on the next.

Neurotoxic and therapeutic effect. The physician then who chooses to ignore the effects on the central nervous system takes a high risk of producing toxic arrhythmias. Is this risk ever justified in the hope of further therapeutic effect? No definite answer can be given to this without an intimate and certain knowledge of the mechanism or mechanisms of the action of digitalis. This is not available but a great deal of information has been accumulated in recent years which will permit the formulation of reasonable working hypotheses.

It now seems likely that there are at least two effects of digitalis: a widespread effect at cell membranes which interferes with the return of potassium to the cell and an intracellular effect in cardiac muscle that in some fairly direct way *increases* the contractility of actomyosin. It would appear that all effects of digitalis on the central nervous system are due to the membrane effect and are associated with intracellular depletion of potassium. The therapeutic contractility effect of the usual digitalis preparations occurs at lower doses at which no depletion of potassium can be measured even by subtle isotope techniques.

In most situations, when neurotoxicity occurs, it can be assumed that a full therapeutic effect has already been achieved. When there is marked intracellular depletion of potassium however such as in severe chronic congestive heart failure or after chronic use of diuretics, then it is possible for neurotoxic symptoms to occur early because of sensitization of the cell membranes to loss of potassium. In this situation the administration of large amounts of oral potassium rather than the use of drugs to mask the neurotoxic symptoms may make it possible to achieve a greater therapeutic effect of digitalis.

Annotations

The platinum electrode

The introduction by Clark and Bargeron[1-3] of the platinum electrode for use in cardiovascular diagnosis represented a major advance in this field. Its practical usefulness, particularly in the detection of small left-to-right shunts, has recently been reported.

Our preliminary experience has been further substantiated in over 200 catheterizations, many of which have been in infants. Of particular interest were two children investigated because of faint diastolic murmurs. At catheterization, identical saturations and normal pressures were recorded throughout the right heart. However, in both children, positive hydrogen curves suggested a small left-to-right shunt, and subsequent retrograde aortography demonstrated a left coronary arteriovenous fistula in one child, and a left coronary artery originating from the pulmonary artery in the other. In two other children with severe infundibular pulmonic stenosis there was no evidence of a shunt in either direction by oxygen saturation data, which with right ventricular pressures over 180 mm. Hg suggested the rare entity of "isolated" infundibular obstruction. However, small left-to-right shunts at the ventricular level were readily demonstrated by hydrogen even though the right ventricular pressure was nearly twice systemic levels. To detect such small ventricular septal defects it is necessary to record the hydrogen curves high in the right ventricular outflow tract since in the body of the right ventricle they may be negative.

Additional uses of the regular single electrode catheter have become increasingly apparent. In the small infant with a large ventricular septal defect, the question of an associated patent ductus arteriosus is frequently a consideration. Unless the catheter is passed through the ductus, other measures are necessary, especially if an open-heart operation is anticipated. The withdrawal of blood for indocyanine curves through a small cardiac catheter is difficult, and angiocardiography is not without risk. However, by means of a No. 4 Lehman catheter a small quantity (50 to 100 mg.) of ascorbic acid may be injected into the arch of the aorta, and if a platinum electrode catheter is in the pulmonary artery the early appearance of indicator is readily detected if there is a left-to-right shunt through a communication between the great vessels. A simple circuit for recording such ascorbic-acid curves has been reported.

The use of ascorbic acid in localizing right-to-left shunts has also been reported.[4,5] We have found that a small platinum electrode attached to a fine wire insulated with Teflon is very satisfactory for recording such curves. The wire is of such size that it is readily passed through an 18-gauge Cournand needle, PE 90 tubing, or directly into an exposed artery pierced with a 20-gauge needle. It is then easily advanced into a central artery and has been found to be useful in all age groups.

We have also passed this wire through the Ross transseptal needle into the left heart for the purpose of detecting mitral insufficiency. Ascorbic acid is injected into the left ventricle via a retrograde catheter and is detected almost immediately by the left atrial electrode if insufficiency exists. If an electrode has also been positioned in a peripheral artery, systemic and left atrial curves may be compared.

Bargeron and associates have placed this Teflon-insulated wire in the pulmonary artery at the time of operation after the repair of septal defects, for the dual purpose of evaluating whether the defect is closed postoperatively and for use as a pacemaker.

Because of the extreme sensitivity of the hydrogen–platinum electrode system, we have found it to be useful in detecting the level of right-to-left shunts, since frequently a very small left-to-right shunt is also present which can be readily detected by the simple technique of inhalation of hydrogen with sampling in the right heart. Generally in patients with large right-to-left shunts the procedure is directed at localizing the level of the shunt by injecting indicator (indocyanine dye, ascorbic acid, cold saline) at various levels in the right side of the heart and sampling from a systemic artery.

An observation made in this laboratory over 2 years ago and also reported by others, is the presence of positive hydrogen curves in the wedge position and distal pulmonary artery in normal subjects. This is useful in confirming the responsiveness of the electrode to hydrogen and has not presented a problem in diagnosis, in that positive curves have not been recorded from the major branches of the pulmonary artery in normal subjects. The positive curves in the wedge position may be a result of the presence of many very small arteries attached like twigs to large-sized arteries capable of holding a catheter in the wedge position. Since these twig-

*Developed by and available from Davis and Geck, Division of American Cyanamid Company, Danbury, Conn., in both 2- and 60-inch lengths.

like vessels immediately break up into capillaries around alveoli, a minimum of reflux would be necessary for inhaled hydrogen to come into contact with electrode in the wedge position. These observations have suggested that the oxygen tension of alveolar gas *may* regulate pulmonary arterial tone directly. It should be noted that, in patients with increased bronchial arterial blood flow, positive hydrogen curves may be recorded in the distal pulmonary arteries.

W tson has recently emphasized the importance of intracardiac electrocardiography particularly in infants. With the platinum electrode one may readily combine the advantages of hydrogen and ascorbic acid with intracardiac electrocardiography.

Clearly the usefulness of this tool in cardiovascular diagnosis and research is just beginning to be realized. Although the hazards of an intracardiac electrode have been re-emphasized[10] the continued appearance of new applications (detecting reflux, aortic insufficiency) indicates the importance of Clark electrode.[11]

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The negative placebo effect in science

The negative placebo effect has been described as follows: If a physician is prejudiced against a drug, the results on administration of the drug will be adverse even if, without his knowledge, a placebo is substituted for the drug. This phenomenon may, at times, be observed in other fields of investigation. It is quite usual, for example, for scientific observations to be tested by experiments which do not repeat the original experiments exactly but instead repeat them either on different species or in different regions or with different techniques. If the worker is prejudiced against the original experiments, the negative placebo effect may induce him, subconsciously perhaps, to choose methods which will obscure the original findings. There is, of course, a positive placebo effect on the part of the original investigator and also on the part of an investigator prejudiced in favor of the original results. This is only too well known, but the negative effect is less often recognized because of the high value placed on the image of the skeptic in the current scientific climate.

It is perhaps worth while, therefore, to repeat certain statistical truisms, namely, that the demon-

stration of a lack of statistically significant separation bet een two groups with respect to a phenomenon may be ttributable merely to inadequacy of methods rather than to the absence of such elationship and that positive observations should be accepted at face value unless failure to confirm rests on exact repetition of the experiments

This is a plea therefore to accentuate the positi but not to eliminate the negative." Multiple failure of confirmation is important, even if the techniques ary but, generally positi onfirma tion even with varying methods should carry more weight.

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Gastric hemodynamics

Within the past several year there has been a renewal of interest in the circulation of the stomach and the relationship of hemodynamics to gastric secretory function. Earlier studies suggested possible dependancy of gastric secretion upon blood flow

The elationship of pressur and flow in the gastric vascular bed has been nvestigated, and there does not appear to be any evidence of autoegulation. Increase in the rate of blood flow to the perfused canine stomach or increase in the pressure gradient across the circulation of the stomach was followed by a decline in gastric vascular esistance.

The response of the gastric vascular bed to series of pharmacologic agents or procedures hich ha n effect on the rate of glandular secretion in the stomach suggests that blood flow may be deter minant of gastric secretion within physiologic limits. Peters and Womack[4] demonstrated that histamine increases the arteriovenous oxygen difference across the canine stomach. They lso showed that the size of glass beads which could pass through the circulation of the stomach was decreased by hista mine. F om this information they inferred that histamine closed large-bor submucosal arteriovenous shunts and redistributed blood to the smaller vessels of the acti ly metabolizing mucosa. Mengzy[6] injected large amounts of histamine and induced systemic hypotension and fall in total blood flow to the stomach blood flow through the actively secreting fundic area of the stomach increased, however t the expense of nonsecreting egions of the stomach. Delaney Weiner and Grim found that histamine increased the diameter of gastric mucosal arterioles and lso increased the amount of K[86] or microspheres hich could be sequestered in the gastric mucosal circulation hile reducing the amounts of these substances collected in the nonsecreting muscular layers of the tomach.

Wangensteen and his associates[1,9] have found increments in total blood flow to the stomach in response to several gastric secretory stimulants, including histamine, serotonin, reserpine, and sympathectomy Conversely inhibitors of gastric blood flow including epinephrine, levarterenol, vasopressin, and vagotomy er associated with diminished gastric secretion. Jacobson[10,11] has demonstrated decrease in gastric ascular resistance in the constant flow perfused stomach in response to the gastric secretory stimulants histamine bradykinin, gastrin and acetylcholine. These tudies and others[12,14] imply relation between gastric blood flow and secretion.

In addition, mechanical increase in blood flow to the stimulated or unstimulated tomach is associated with an increase in the olume of gastric secretion[13,16]

These studies ha e not been able to exclude the possibility that physiologic or pharmacologic stimuli to gastric secretion may act directly upon oxyntic cells, and that increased blood flow may be either a local supporti response to the enhanced metabolic acti ty of hypersecretion or *pari passu* another unrelated action of many gastric secretory stimulants. Resolution of this dilemma has been hampered by the lack of adequate methods for a continuous measurement of gastric mucosal microcirculatory hemodynamics. Perhaps the recently described thermocouple technique of Demling and Wachsmann[16] may provide better pproach to this problem.

The clinical implications of relationship between blood flow and secretion in the stomach are intriguing Womack and his associates[17] reported successful treatment of 2 patients with massive hypersecretion by means of ligation of part of the arterial inflow to the stomach. Older experiments, however failed to demonstrate any protectiv effect of surgical eduction in blood flow upon the production of experimental peptic ulcers.[18]

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Physiologic basis for the normally low oxygen content of coronary venous blood

Little en on by way of explanation has been given to the well known fact that in man and in nes betized or nane-thetized dogs the coronary mus blood has the lowest oxygen content (5 olumes per cent or ss son (25 per cent) in comparison with the venous blood of other organs of the body The only reference of which the author is aware is that of Gregg who stated, "The very high oxygen extraction from the myocardial capillaries a compared with other vascular beds could result from relatively low blood velocity high metabolism, or high level of vascularity the latter two of which are known to be high compared with other tissues.

This explanation, although basic ppeared to be ncomplete and required further elaboration. The observation that the myocardium is richly supplied with capillaries has been generally recognized. This by itself would tend to reduce the capillary blood velocity by increasing the total capillary cross-sectional area, provided that all other factors were to remain equal (coronary blood flow perfusion pressure extravascular compression, myocardial oxygen demand, etc). However when tissue has more capillaries, it will have a greater flow of blood because of reduction in the total vascular resistance (other things being equal). Consequently capillary blood velocity will depend on the quantitative relation between increase in flow and increase in total cross-sectional area of the capillaries. Unfortunately there are no data on the mean velocity of blood in the coronary capillaries.

The oxygen demand of the pumping myocardium in situ is one of the highest approximately 10 to 15 ml. per minute per 100 grams of tissue This would undoubtedly contribute to the high extraction of oxygen, but it cannot entirely explain the low coronary venous saturation since other organs (e.g thyroid, adrenal, brain) also have high oxygen uptake yet their venous oxygen content is much higher than that of heart muscle. An additional factor would be that the total flow through the myocardial capillaries per unit time is somewhat restricted in relation to the demand of the rhythmically contracting heart muscle cells. If this concept is accepted one must seek explanation for the

restriction of the coronary blood flow under normal conditions. The most plausible explanation appears to be that the beating ventricles which develop high intramyocardial pressure during systole[8,9] compress the intramural vessels and curtail the flow. In support of this view are the observations of Sabiston and Gregg,[10] who noted that asystole induced by vagal stimulation produced a 50 per cent increase in the flow of blood through the perfused coronary arteries, despite the fact that myocardial oxygen demand is greatly diminished and the vagus presumably has a direct constrictor action on the coronaries. It was concluded that the net effect of repeated contractions was to impede the over-all coronary flow. In other words, the impediment to coronary flow during systole apparently is not compensated for during the period of diastole.

Further support for the explanation given above comes from the observation that skeletal muscle during repeated tetanic contractions (as in muscular exercise) increases its extraction of oxygen from the perfusing blood, causing its venous oxygen to approach or equal the oxygen content of the coronary venous blood (7 to 3 volumes per cent).[11] Here too the increase in flow through active muscles does not parallel the increase in oxygen demand, presumably on account of the impediment to flow by the contracting muscle fibers.

If the foregoing thesis is accepted, one should explain the fact that in the denervated heart-lung preparation which is pumping blood against normal levels of aortic pressure the coronary venous oxygen content is relatively high (8 to 10 volumes per cent). The possible reasons for this are: (1) The metabolic rate (hence, the oxygen demand) of the isolated perfused working heart is lower than that of the innervated heart beating in situ. The reasons for this difference are not yet clearly defined. (2) Denervation of the heart may dilate the coronary vessels by removing a net tonic vasoconstrictor influence (?). (3) Biochemical abnormalities in the perfusing blood may have a direct dilator action on the coronaries (?). In the present state of our knowledge it is impossible to assess the relative influence of each of these factors.

The concept advanced above does not necessarily imply that cardioacceleration should have a restrictive effect on coronary flow. Most investigators[12] have noted that tachycardia increases coronary blood flow. This may be explained on the basis that under these circumstances the dilator action of metabolites from increased metabolic rate outweighs the effect of shortening of the period of diastole.

Before accepting the concept of restriction of coronary flow it is necessary to consider the possible role of arteriovenous shunts as the basis for the differences in the oxygen content of venous blood in various tissues. If it is assumed that blood flowing through arteriovenous shunts does not participate in gaseous exchange, tissues that have numerous functional arteriovenous shunts should have a high venous oxygen content, and vice versa. Can one demonstrate that the thyroid, the adrenal, the brain, etc., have many more functional arteriovenous shunts than does the heart? To our knowledge, no shunts have been demonstrated in adrenal or brain tissue, either by histologic or physiologic methods. Modell[?] has described arteriovenous anastomoses, mostly of capillary dimensions, in the thyroid gland of the dog. Whether such vessels deliver oxygen to the cells of the thyroid remains a problematic question. According to MacLean and associates[?] arteriovenous shunts larger than 20μ account for about 5 per cent of total coronary inflow to the right heart. From such considerations it is very unlikely that differences in the amount of blood flowing through arteriovenous shunts, if these exist, can account for the variations in the venous oxygen content of different tissues.

In conclusion, it may be stated that the normally low oxygen content of coronary venous blood is related primarily to the contractile activity of the myocardium (which augments the demand and curtails the supply of oxygen) against a background of neurogenic influences and homeostatic conditions to which the intact normal heart is constantly subjected.

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Letter to the Editor

Bradykinetin rather than bradykinin

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March 4, 1963

To the Editor

From a recent review[1] and previous editorial[2] upon the subject of bradykinin, it has become clear that this endogenous nonapeptide with great biologic activity is one of the plasma kinins,[3,4] the first to be fully elucidated chemically and synthesized in the Sandoz laboratories in May, 1960.

However any new name or term must be endowed with precision, and must be free from confusion: plasma kinins, bradykinin and allied terms (*bradykininogen*, etc.) have to be changed.

Indeed, when Rocha e Silva, Beraldo and Rosenfeld[5] (1948) described a new active biogenic substance which caused slow contraction of isolated intestine, they gave to that new substance the name *bradykinin* from the Greek words *βραδύς* (slow) and *κινεῖν* (to move).

But in the Greek language such a word composed from an adjective (*βραδύς*) and the infinitive of a verb (*κινεῖν*) is untenable: the proper terms in discussion are *bradykinetin*, *plasma kinetins*, *bradykinetinogen*, etc.

This seems imperative in order to avoid confusion which, unfortunately, has already come into play with the appearance of pertinent articles in Italian, in which language the word *bradykinin* has been translated as *bradychinina*, a name that suggests quinine which is known as *kinina* in Italy. In this last instance the term *bradychinetina* would seem to be more suitable and/or correct.

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Book review

ADVANCES IN CARDIOLOGY (*Fortschritte der Kardiologie*) (Progrès en Cardiologie). Volume 3. Chirurgie du Coeur (Bibliotheca Cardiologica, fasc. 12). By Ch. Hahn, Lausanne, Switzerland, and A. G. Brom and J. Nauta, Leyden, *Holland. Basle, 1962*, S. Karger (in U. S. A. Albert J. Phiebig, P. O. Box 352, White Plains, N. Y.), 398 pages, 285 illustrations. Price $18.50.

This book, which presents the views of the Leyden School on cardiac surgery and surgical cardiology, according to the authors' own statement is written in French and comprises three sections: congenital cardiac malformations, acquired lesions, and general considerations in regard to open-heart surgery.

The two first sections discuss successively symptomatology, special investigations, and surgical indications, tactics, and techniques.

Section I, which is by far the largest one (273 pages), covers a good many—*but not all*—congenital malformations that cardiologists and surgeons have to handle. Symptoms and clinical signs are generally presented in a clear and accurate, *but rather fragmentary way. For example,* the murmurs are superficially described and the features which often permit a sound approach to differential diagnosis on purely *clinical grounds are somehow neglected. Little stress is* put upon the difficulties that the clinician encounters in distinguishing between the continuous murmur of patent ductus arteriosus, the jugular venous hum, *and other systolo-diastolic* murmurs which mimic patent ductus.

With a few exceptions, electrocardiographic and vectorcardiographic descriptions are rudimentary; radiologic data are better presented. Much attention is paid to phonocardiography and sphygmography in the diagnosis and localization of several lesions, especially vascular stenoses. Angiocardiographic contributions are modest, with few illustrations. As to cardiac catheterization studies, it seems to me that they were carried out by means of time-honored classic method, but no mention is made of the more modern tools (dye-dilution curves, radioisotopic, nitrous-oxide, and platinum-electrode techniques) now in current use in well-equipped centers to detect, localize, and quantitate intracardiac and intervascular shunts at any level.

Original and provocative concepts on the embryology of the interauricular septum are proposed, whereby the septum secundum is denied existence, being but a fold; hence a new classification of atrial septal defects into dorsal type (septum secundum) and ventral type (septum primum).

The parts which deal with discussions on indications for surgery are very good and the decisions suggested sound quite wise. A large place in every subsection is allowed for details *of surgical techniques. They concern more directly heart surgeons than cardiologists.*

Section II is practically nonexistent, being made up merely of some 25 pages of commonplace presentation of three acquired heart diseases: aortic stenosis, mitral stenosis, and constrictive pericarditis.

Section III summarizes in a clear, detailed, although concise and accurate, way a good *number of facts related to the protean facets of open* heart surgery, deep general and selective hypothermia, anesthesia, and preoperative and postoperative care. Of course these 55 pages will *teach little either to surgeons or to anesthesiologists*, but they might be fruitfully read by cardiologists and internists for the clarification of their understanding of those complex matters.

I have appreciated the short but excellent chapter which outlines secondary pulmonary hypertension—although the anatomic concept *of a hypertrophied muscular coat* of the pulmonary *arterioles* is open to debate (Rushmer).

The printing and illustrations are good. Strangely enough the bibliography is inappropriate, being limited to an alphabetical list located at the end of the book (instead of a bibliography at the end of each chapter), without any numerical references throughout the text. Therefore it is hardly usable.

On the whole, the main criticism of the book is that it looks somewhat like a hybrid: too big as a primer, too short as a textbook to deserve its ambitious title ("Heart Surgery"). In fact, it serves chiefly as a testimony to the very valuable work being performed in the field of (congenital) heart surgery by an active and well-organized European group.

Table I. Response to Valsalva maneuver in normal subjects

Case	Age Sex	Brachial arterial pressure (mm. Hg)			Heart rate		
		Rest	Strain	Overshoot	Rest	Strain	Overshoot
1	12 M	154/62	69/49	179/75	92	123	71
2	12 F	134/62	75/57	185/90	95	143	57
3	15 F	117/74	84/63	144/86	100	129	62
4	15 M	134/65	84/55	208/109	67	110	53
5	16 M	149/70	150/95	175/84	79	104	61
6.	17 F	132/68	94/78	175/99	133	167	96
7	18 F	151/81	115/84	201/102	79	133	72
8.	18, M	148/75	95/69	210/111	75	108	60
9	18, F	123/74	99/73	153/87	75	121	54
10.	20 F	120/66	98/76	138/82	62	99	56
11	22 M	150/83	124/88	157/91	83	113	58
12	23 M	148/86	116/94	176/96	79	113	44
13	23 M	146/84	129/84	192/109	67	92	47
14	25 M	136/76	145/91	157/86	71	93	63
15	25 F	150/85	88/72	234/123	92	143	53
16.	26, M	137/80	106/70	169/92	69	107	51
17	29 F	131/70	76/61	186/102	91	128	50
18.	30 M	122/67	106/79	176/102	73	120	58
19	34 M	144/94	158/119	158/101	72	87	62
20	54 M	137/76	127/85	177/91	96	115	68
21	8 F				72	75	70
22.	8 M				90	120	81
23	9 M				108	110	73
24	9 M				80	108	65
25	11 M				60	105	60
26.	11 M				90	140	55
27	12, F				78	100	57
28.	12 F				95	130	85
29	12 M				105	150	85
30	13 F				85	140	67
31	14 M				90	120	56
32	18, F				90	110	45
33	23 F				63	95	60
34	23 F				75	110	55
35	28 M				80	88	65
36.	28, M				53	89	49
37	29 M				50	75	47
38	29 M				70	85	63
39	30 M				65	85	57
40.	30, M				70	103	66
41	31 M				60	68	51
42	31 F				80	140	65
43.	33 F				70	75	68
44	34 M				70	87	55
45	34 M				60	65	53
46.	35 F				75	85	65
47	35 F				75	105	70
48	38 M				67	120	50
49	39 F				75	95	65
50	45 F				90	110	75

other of these is at least 15 per cent altered from the resting value.

All but one of the normal subjects met these criteria, whereas only 5 of 36 patients with atrial septal defect did so. These 5 patients with clearly normal responses are therefore the false-negative cases in the use of the Valsalva maneuver in de-

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*January, pp. 1-144; February, pp. 145-290; March, pp. 291-432; April, pp. 433-578; May, pp. 579-722; June, pp. 723-844.

Subject index*

tecting atrial defect, and are here briefly mentioned individually additional data are given in Table III Four have presumably small defects with little or no cardiac enlargement

Case 11 This 21 year-old tudent th no symptoms was studied because of Grade 2 pulmonary systolic murmur which was first heard when he was 6 years old. Chest -ray films, electrocardiogram, and the second sound on auscultation were considered to be probably normal, but small shu t was found t the trial level, nd the catheter entered the left trium nd pulmonary veins. Oper tion was considered unnecessary

Case 15 This 27 yea -old housewife was referred for investigation of Grade 2 pulmonary systolic murmur which had first been noted on a routine prenatal examination 2 years previously The elec trocardiogram and the second sound on ausculta tion were considered t be probably normal but -ray films showed slight cardiac enlargement and pulmonary plethora. There was small shunt t the trial level and the catheter entered the left trium. Operation was considered unnecessary

Case 19 This 35-year-old housewif had mur mur which was first noted when she was 6 months old but there had been no symptoms until recent paroxysmal tachycardia. There was a Grade 3 pulmonary systolic murmur pulmonary sy tolic ejection sound nd wide fixed splitting of the second

Table II *Response to Valsalva maneuver in atrial septal defect*

Case	Age Sex	*Brachial arterial pressure (mm Hg)*			*Heart rate*			*L R shunt* (%)
		Rest	*Strain*	*Overshoot*	*Rest*	*Strain*	*Overshoot*	
1	9 F	129/72	131/78	131/70	109	114	112	66
2.	12 F	—	—	—	94	107	90	44
3	13 M	137/75	138/73	156/86	92	109	74	47
4.	15 F	134/74	145/88	140/81	70	73	72	66
5	17 F	109/59	99/56	104/57	78	90	95	63
6.	17 F	130/76	132/88	142/85	86	118	86	90
7	18, M	122/71	131/86	136/84	86	90	80	65
8.	19 F	133/68	152/77	145/81	74	90	73	—
9	21 F	120/85	125/85	128/88	86	74	72	56
10.	21 M	125/80	133/85	125/78	60	61	64	73
11	21 F	143/80	123/94	179/93	83	113	71	42
12	22 F	132/83	149/97	133/84	70	79	78	79
13	24 M	136/78	147/90	145/95	81	84	71	83
14	27 F	112/68	120/85	117/77	114	109	118	71
15.	27 F	128/71	95/68	180/96	82	109	65	39
16.	29 F	125/60	126/83	128/77	70	89	70	83
17	30, F	156/77	173/95	162/79	70	85	74	70
18.	30 F	119/73	119/79	126/83	97	120	109	67
19	35 F	149/94	136/93	172/112	105	119	78	58
20.	35 F	123/73	81/67	160/87	118	153	129	47
21	35 M	113/61	131/79	113/61	77	81	78	76
22.	37 M	138/71	119/76	154/77	72	76	79	41
23.	38, F	117/26	124/93	116/77	86	94	81	77
24	38, F	154/81	152/89	154/78	73	74	68	26
25	39 F	143/72	131/84	158/84	65	78	69	62
26.	40, M	140/76	121/73	160/91	93	102	71	19
27	40 M	117/67	112/72	118/63	98	100	100	53
28.	42 F	91/52	100/62	86/48	46	44	47	55
29	44 F	150/93	154/100	157/97	82	82	83	61
30.	44 F	136/81	156/117	133/83	65	73	68	74
31	45 F	133/92	101/85	177/109	110	123	91	52
32.	46 F	134/73	124/85	142/80	93	100	86	70
33	50 F	—	—	—	72	72	70	70
34	52 F	141/85	107/85	156/85	97	98	91	70
35	55 F	127/67	123/80	133/73	70	83	69	32
36	58, F	136/81	120/87	150/87	90	100	92	86

Case 2 Ostium primum defect without ventricular defect or mitral insufficiency *Cases 18, 19 and 33* Mild stenosis of pulmonary valve as well as atrial defect. *Case 34* Severe pulmonary hypertension and bidirectional shunt. *Case 19:* History of overt congestive heart failure.

Table III Data in 5 patients with atrial septal defect and normal Valsalva response

	Case 11	*Case 15*	*Case 19*	*Case 26*	*Case 31*
Superior vena cava					
O_2 content (vol. %)	12 5	13 4	12 6	14 7	12 6
Inferior vena cava					
O_2 content (vol. %)	11 4	14 4	—	—	15 3
Right atrium					
O_2 content (vol. %)	13 4	15 1	13 9	15 0	14 7
Pressure (mm Hg)	8	6	5	2	1
Left atrium					
O_2 content (vol %)	15 9	16 8	—	—	—
Pressure (mm Hg)	9	7	—	5	7
Pulmonary artery					
O_2 content (vol %)	14 1	15 0	14 2	16 0	16 4
Pressure (mm Hg)	29/10 16	20/7 13	25/10 15	17/7 12	43/19 32
O_2 capacity (vol. %)	17 3	17 6	15 8	20 5	19 7
L R shunt (%)	42	39	58	19	52
Heart size (CTR)†	Normal (47)	Slightly large (49)	Normal (47)	Normal (44)	Moderately large (51)
Pulmonary vessels	Probably normal	Slightly full	Normal	Normal	Moderately full
P R interval (sec.)	0 20	0 20	0 15	0 20	0 16
Q-S duration	0 09	0 09	0 09	0 10	0 09
V pattern	RSr′	rSr	Rs	rsr′	rsr′
A -P interval (sec.)	0 04	0 04	0 07	0 04	0 04

Pulmonary edge pressure
†Qualitative estimate of heart size in the frontal view with transverse cardiothoracic (CTR) ratio in parentheses.

sound The electrocardiogram showed right ventricular hypertrophy and the x-ray film showed marked dilatation of the pulmonary trunk, although there was no cardiac enlargement or pulmonary plethora. In addition to the modest shunt at the atrial level there was a pulmonary valvular peak systolic gradient of 26 mm Hg mild stenosis of the pulmonary valve, as well as atrial septal defect, was considered likely Operation was suggested but has not so far been accepted.

Case 26 This 40-year-old airline employee was seen for functional symptoms related to anxiety He had a Grade 2 pulmonary systolic murmur which had first been noted during selective service examination 22 years previously Chest x-ray films electrocardiogram and the second sound on auscultation were thought probably to be normal. The shunt at the atrial level was small, and operation was considered unnecessary

Case 31 This 45-year-old housewife who was referred for treatment of asthma, bronchiectasis, and paroxysmal tachycardia, was found to have typical atrial septal defect as well. This was confirmed by operation under direct vision

Cases 11 15 and 26 are particularly interesting since their clinical features might have been considered to be normal and the Valsalva response might have served to confirm this impression However all 3 had rr′ patterns in Lead V_1 of the electrocardiogram P R intervals of 0 20 second and relatively fixed separation of aortic and pulmonic closure by 0 04 second in the phonocardiogram In the present group of patients with proved atrial defect the response was abnormal in 10 of 15 with less than a 60 per cent left to-right shunt and abnormal in 7 of 11 with transverse cardiothoracic ratios less than 50 per cent Marked cardiac enlargement or a very large shunt is, therefore not necessary in the production of this phenomenon

Factors influencing the response. The physiologic effects which follow on the performance of the Valsalva maneuver are complex and measurement of the heart rate and arterial pressure is a very indirect method of assessing the effects, which are primarily those of diminished venous return diminished cardiac output and peripheral vasoconstriction To aid in the interpretation of the data somewhat we studied the role of body position and the role of the experimental conditions of cardiac catheterization on the Valsalva response

Thirty-three subjects were tested in the supine and upright positions, the electrocardiogram being used to measure the heart rate response only. This group included 20 normal subjects and 13 patients with various forms of heart disease other than atrial septal defect. The bradycardia during the overshoot period was less when the subjects were in the sitting position but by an average of only 2 per cent, 20 of 33 showing a lesser bradycardia, 1 the same degree, and 12 a greater overshoot bradycardia while sitting. The tachycardia during the strain was less in 20 of 33 subjects when they were sitting up, no different in 4, and greater in 9; the average change for the whole group was a lesser tachycardia by 9 per cent in the sitting position.

In 19 subjects the Valsalva response was tested during cardiac catheterization with arterial puncture and also with the electrocardiogram only in ambulatory conditions on a different day to assess the effect of these differing conditions. This group included 2 normal subjects and 17 patients with various forms of heart disease, including 9 with atrial septal defect. Tachycardia during the strain was greater by an average of 6.5 per cent during catheterization, 14 of 19 patients showing a change in this direction. Bradycardia during the overshoot period was greater during catheterization in 10 of 19, by an average of 2 per cent.

Discussion

These results amply confirm the observation of McIlroy that the Valsalva response may be "square wave" in some patients with atrial septal defect without heart failure, but further show that the response is abnormal in a less striking way in the majority of patients when compared quantitatively with normal subjects. The rarity of overt heart failure in this group of patients supports the thesis that the abnormal Valsalva response does not result from myocardial failure in this instance but from the abnormally large volume of blood pooled in the heart and lungs, allowing substantial systemic cardiac output to continue despite interruption of venous return. The relatively small shunts and slight cardiac enlargement in the exceptional cases with normal responses also support this thesis.

The hope that this test would prove to be a simple and useful one for ruling in or out atrial septal defect in ambulatory patients was only partially realized since there were about 15 per cent false negative results, and, of course, there will be many false positive ones, the phenomenon being in no way specific for atrial septal defect. The empirical value of the test is well defined by the data obtained. About 86 per cent of patients with atrial defect show an abnormal response if both heart rate and direct arterial pressure are measured and about 75 per cent show an abnormal response if the electrocardiogram is used to measure heart rate only. An abnormal response in patients in whom atrial defect is suspected indicates the need for further investigation. A normal response in patients in whom atrial defect is suspected does not rule out this condition, but, when combined with other evidence, may be helpful in avoiding unnecessary cardiac catheterization in some of the many persons with pulmonary systolic murmurs and split second sounds, prominent pulmonary vessels, and electrocardiographic patterns suggestive of incomplete right bundle branch block. The test is also helpful in assessing the result of surgical closure of atrial defect.

The normal response to the Valsalva maneuver is highly variable and the factors in this variability are not easy to assess. We found generally greater responses during arterial puncture and cardiac catheterization than during the simple electrocardiographic test, a difference which was probably due to different selection of normal subjects as well as to different conditions of the tests.

Summary

The response of the heart rate and arterial pressure to a standard Valsalva maneuver was studied in 36 patients with atrial septal defect and compared with that in 50 normal subjects. A quantitative method for describing the response was devised.

The normal response was rather variable but all normal subjects showed some narrowing of pulse pressure during the strain

and some systolic pressure overshoot in the period after release In every normal subject the narrowing of the pulse pressure during the strain or the systolic pressure overshoot was a change of at least 15 per cent from the control value The changes in pressure were accompanied by tachycardia during the strain and brady cardia during the overshoot period and the strain tachycardia or the overshoot bradycardia was at least 10 per cent altered from the control value in all normal subjects.

By these criteria 31 of 36 patients (86 per cent) with atrial septal defect showed abnormal responses, and in 27 of 36 (75 per cent) this was evident in the heart rate response so that this test could be used to some advantage as a simple screening test of outpatients with the electrocardiogram The abnormal response is presumed to result from the increased intrathoracic blood volume allowing adequate cardiac output to continue despite temporary obstruction of venous return rather than from myocardial failure which was not present in these patients.

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Experimental and laboratory reports

The diacardiac phonogram

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The conduction of sound through the walls of the different cardiac chambers and great vessels occurs under physiologic and pathologic conditions. It is one of the main factors which influence the frequency intensity spectrum of heart murmurs in so far as they are picked up outside the heart. Therefore, it is of special interest for the rational interpretation of the phonocardiogram to know the laws which apply to the conduction of sound through the cardiac walls.

Feruglio was the first to publish a method by which the transmission of sound could be investigated experimentally. He produced sound waves by means of a special turbocatheter and recorded the acoustical signals at the thoracic surface.

For some years we have dealt with the same problem but because we could not find a sound generator suitable in size to put into the heart and able to produce sound waves of definite intensity and frequency, we tried the reverse way. Referring to the Reziprozitätstheorem of von Helmholtz, we put the sound generator against the thoracic wall and picked up the signals inside the heart cavities in men and animals.

By this method we were able to apply any frequency with controlled intensity to each point of the body surface and by means of a phonocatheter of known frequency response and sensitivity to record the transmitted signals inside the different heart cavities and great vessels.

During the course of our studies it became evident that apart from phonocardiographic aspects *sound conductivity* of the different heart chambers *will change during cardiac activity* and *will reflect a special heretofore not measured mechanical property of the heart muscle and vessel walls* which may be of physiologic and pathologic significance.

The pattern which represents the variations of sound conductivity during the cardiac cycle will be called the *diacardiac phonogram*.

Methods

The principle of the method is illustrated in Fig. 1 and published in detail elsewhere.

As a source for sinusoidal vibrations we used a tape record with the standard test frequencies 50, 80, 100, 160, 200, 320, 400, 600, 800, *and* 1,000 cycles per second. We also employed a sound generator which allowed a choice of any frequency between 3 and 1,300 c.p.s. (Type Z 906).

The electrical vibrations could be amplified by means of a two-stage RC-coupled pentode amplifier with negative feedback, or a manufactured amplifier Type GM 5535 which produced constant output voltage and current without respect to

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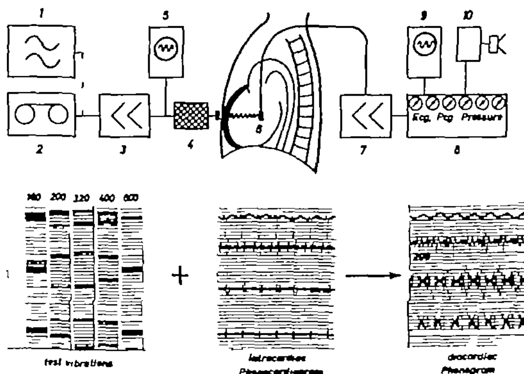


Fig. 1. Schematic representation of the method used for the investigation of the conduction of sound through the heart walls. *1,* Sound generator. *2,* Tape recorder. *3,* Preamplifier. *4,* Electrodynamical sound transducer. *5* and *9,* Oscilloscopes. *6,* Phonocatheter (intracardiac sound receptor). *7,* Preamplifier. *8,* ECG sound, and pressure recorder. *10,* Loudspeaker.
Below the diagram on the left. Some test frequencies recorded by means of the low-, middle-, and high-frequency filter of the Atlas phonocardiograph before transmission through the cardiac walls. Numbers at the top indicate cycles per second. *Center,* Normal right atrial intracardiac phonocardiogram (rabbit). *Right,* Test vibration (200 c.p.s.) after transmission through the heart walls superimposed on intracardiac phonocardiogram and modulated by cardiac action = diacardiac phonogram.

frequency. The electrical signal was fed into an electrodynamic transducer (Type PR 9261 or PR 9270),* which could be adapted to the chest wall by constant pressure. The energy output was set at 2 watts.

The transmitted signals were picked up inside the heart chambers and vessels by means of a phonocatheter described by Wallace and associates.[5] The barium titanate receptor was coupled to a self-built preamplifier[3] with a very high signal-to-noise ratio. The preamplifier was fed into a four-channel or six-channel Atlas photographic recorder which split the sounds into 3 to 6 frequency bands according to the method of Maass and Weber. The diacardiac phonogram could be recorded simultaneously with the electrocardiogram, the extracardiac phonocardiogram, the intracardiac pressure, and the respiration.

Vibrations, before and after transmission through the heart walls, could be observed visually and acoustically by means of oscilloscopes and loudspeakers.

Results

1. The heart chambers and vessels investigated (superior and inferior venae cavae, right atrium and ventricle, pulmonary artery, and aorta) allow the sound waves to pass through their walls within the tested frequency range (50 to 1,000 c.p.s.) as far as intensities are applied to the chest wall which are comparable to those normally or pathologically generated within the heart.

2. During induced cardiac standstill as well as post mortem (animal experiments) the transmitted sound waves are

*Supplied courtesy of Elektro-Spezial G.M.B.H., Hamburg.

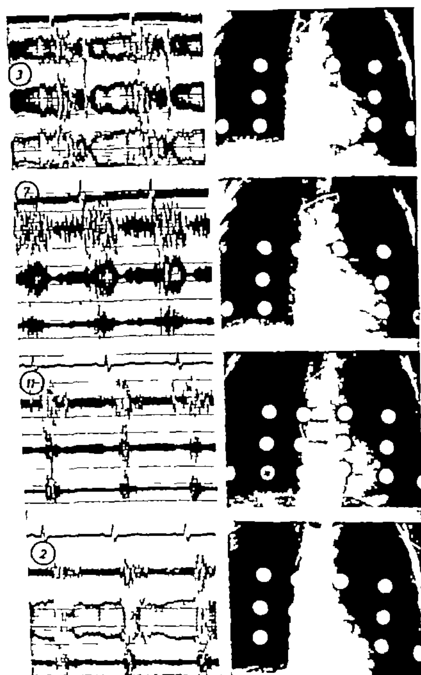


Fig. 2 Typical pattern of the diacardiac phonogram picked up in the different heart cavities, pulmonary artery, right ventricle, right atrium, superior vena cava. Encircled numbers refer to the corresponding numbers on the x-ray pictures, which also indicate the position of the sound generator. Test vibrations of constant strength and frequency (200 c.p.s.) at the different locations. Phonogram recorded with the low-, middle-, and high-frequency filter of the Atlas recorder according to the method of Maass and Weber. The mesosystolic vibrations, seen especially in the atrial and vena caval records, correspond to the murmur of congenital aortic stenosis which is conducted to the different cardiac chambers[3] (10-year-old boy).

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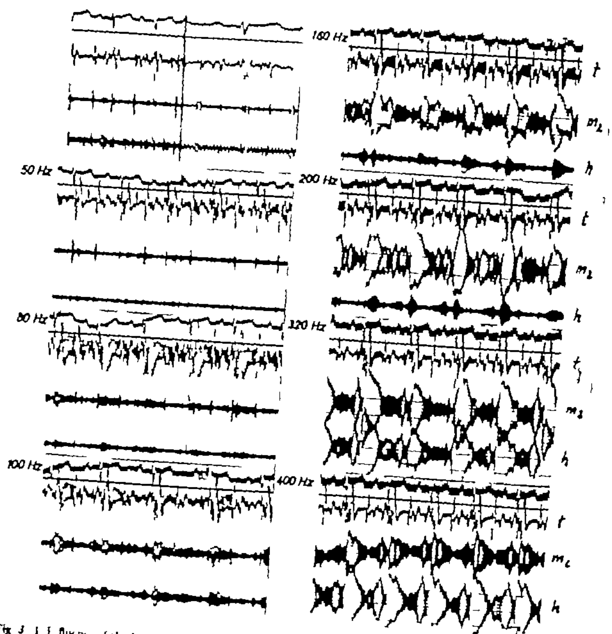


Fig 3 I I fluence of the frequency of the test vibration—indicated at the top of all tracings in cycles per second (H)—on the diacardiac phonogram recorded within the right ventricle. Constant position of sound generator and sound receptor in 4½-year-old boy with tetralogy of Fallot \ spontaneous murmur within the right ventricle (see upper tracing on the left). B (see opposite page) I fluence of the frequency of the test vibration on the diacardiac phonogram of the right ventricle 4 bm Position of the phonocatheter in respect to the point at which the sound generator has been adapted. (Same boy as in Figs 2 and 4)

of constant intensity and therefore form a continuous band of vibrations on the intracardiac record The amplitude of this band depends on the frequency and intensity of the sound which is generated the damping factor of the interposed tissues and the known frequency response of the sound receptor used and the high pass filters of the recorder

3 *Cardiac action* modifies the amplitudes of the sound waves transmitted from the chest wall to the interior of the heart chambers and vessels. The recorded pattern shows striking variations of sound conductivity and is of different shapes in the different heart cavities and vessels. Although the amplitude modulation of a sound wave passing the venae cavae or

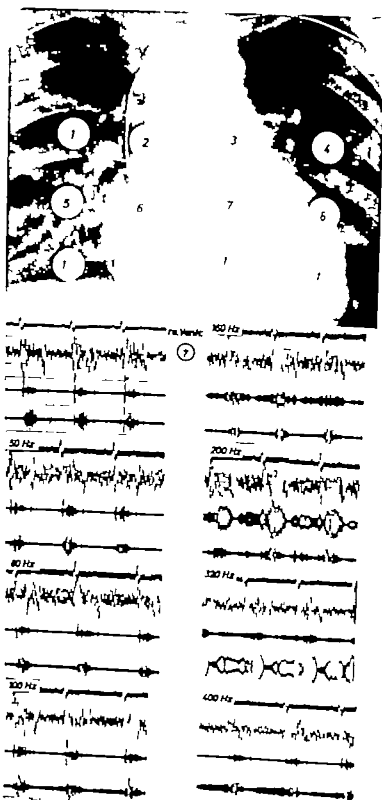


Fig. 3, B. (For legend see opposite page.)

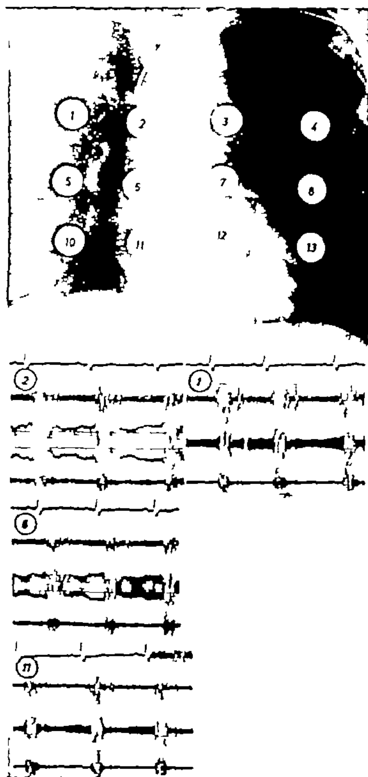


Fig. 4. Influence of different positions of the sound generator on the diacardiac phonogram recorded in the superior vena cava. Constant test frequency (200 c.p.s.) and intracardiac receptor position. Numbers at the top of the tracings indicate the positions of the sound generator which correspond to the same numbers on the x-ray picture. Same boy as in Fig. 2. Systolic murmur of aortic stenosis superimposed on the tracing.

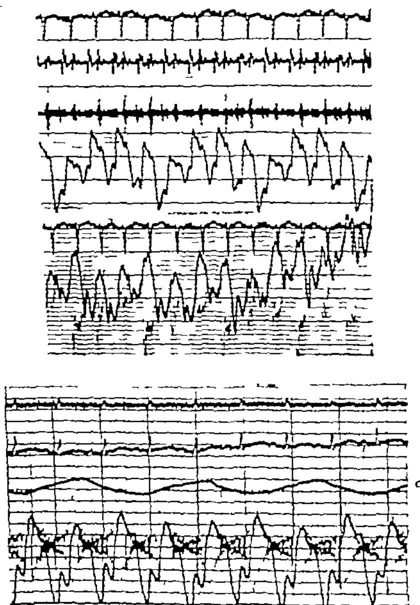


Fig. 5. *A*, ECG, intra-atrial phonocardiogram, and right atrial pressure with pronounced variations in respiratory pressure (rabbit). *B*, ECG, right atrial pressure, and diacardiac phonogram of the right atrium. High amplification of the sound tracing so that only the upper half of the vibrations is to be seen. *The shape of the upper outline of the sound tracing is discordant with the fluctuations in atrial pressure and reflects the respiratory variations only to a minor degree* (rabbit). *C*, Simultaneous recording of the ECG, the *respiration*, the diacardiac phonogram of the right atrium, and the right ventricular pressure. Test frequency 200 c.p.s. The diacardiac phonogram shows no definite respiratory variations.

pulmonary artery is only of minor degree it is strongly marked in the ventricle (see Fig 2) On the other hand the typical pattern for a given heart cavity is only little affected by the frequency of the transmitted sound wave within the investigated frequency range (see Fig 3 *A* and *B*)

4 The mean level of intensity of the diacardiac phonogram is a function of the distance between the sound generator and receptor i e of the location of the sound generator if the receptor is held in constant position (see Fig 4) When the distance between sound generator and receptor is increased the amplitude of the recorded sound waves rapidly decreases The point of optimum transmission is approximately that of the shortest distance between sound generator and receptor Further studies are to be made in order to check inhomogeneities of the sound field

5 Respiration has little influence on the diacardiac phonogram in respect to the specific cardiac effect on the transmission of sound if the sound generator is adapted to precordial areas which are normally used for auscultation (see Fig 5)

Discussion

The ability of the heart chambers and vessels to allow the passage of sound waves within the tested frequency range (50 to 1 000 c p s.) is not surprising because this is a supposition for the well known transmission to the thoracic surface of murmurs which originate within the heart.

In this respect the value of the method described is the possibility exactly of investigating the behavior of the conduction of sound to and through the heart for any frequency and to measure the influence of the distance between the source of sounds or murmurs and the location of the microphone With reference to the Reziprozitätstheorem of von Helmholtz it is possible to explore the correlations between the area of best audibility of a sound phenomenon and the heart chamber in which it originates.

The variations in sound conductivity from the chest wall to the cavities of the heart during cardiac activity which seemed to be characteristic for the different heart chambers, are a completely new aspect of cardiac function The type and degree of these variations in sound conductivity may be related (1) to cardiac factors, such as (a) different stiffness of the heart muscle walls during contraction and relaxation (actual intracardiac or transmural pressure) (b) basic compliance or elasticity of the heart chambers in question (muscle tone) (c) thickness of the heart wall (hypertrophy) (d) changes in volume of the heart cavities, (e) displacement or rotation of the heart in respect to the sound generator (2) to extracardiac factors, such as (a) varying distance between the chest wall and the heart caused by respiration (b) changes in sound conductivity of the lung or other extracardiac tissues.

The fact that only small displacements of the sound receptor (e.g from the pulmonary artery to the outflow tract of the right ventricle or from the right ventricle to the right atrium)—leaving the extracardiac conditions almost unaffected—do alter the diacardiac phonogram very markedly and that, moreover different locations of the sound generator do not influence significantly the typical pattern for a given heart chamber seems to indicate that the variations in sound conductivity are due mainly to cardiac factors, which are related to the mechanical activity of the heart.

Fig 5 shows a reciprocal relation between the sound conductivity of the right atrial wall and the pressure fluctuations in the right atrium It is also apparent that the diacardiac phonogram shown is affected to only a very small degree by the respiratory variations of the right atrial pressure. The same may be seen in Fig 5,*B*

Further studies are needed, and are already in progress to clarify the determining factors of the diacardiac phonogram and to test its diagnostic usefulness.

Summary

1 A method is described which allows the study of the transmission of sound from the surface of the body to the interior of the different heart cavities and vessels in animals and human beings.

2. During cardiac standstill as well as post mortem there is a conductivity of sound waves from the chest wall to the interior of the heart and vessels (within